

Inverse Electron Demand Diels-Alder Chemistry of Electron Deficient Chromone-fused Dienes

By

Amaizu Joseph Nwagbara

B.Sc., Hons. (2009), Abia State University, Nigeria

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Dedication

To the memory of my late parents

(His Royal Majesty Eze and Ugoeze Roseline Nwagbara)

Abstract

An introduction to inverse electron demand Diels-Alder reaction (IEDDA) chemistry is presented in Chapter one. In Chapter two, work aimed at improving an IEDDA-driven domino reaction leading to 2-hydroxybenzophenone is presented. Chromone-fused electron deficient dienes were synthesized as substrates for IEDDA-driven domino reactions. The reaction between one of these dienes and *in situ*-generated enamines of cyclobutanone was optimized. The optimized conditions were then applied to a variety of enamines derived from piperidine and various ketones (cyclic and acyclic). In almost all cases, the yields were superior to those obtained using preformed enamines and previously reported conditions for the *in situ* formation of the enamine.

In Chapter three the attempted synthesis of a new chiral $[n](1,6)$ pyrenophane is described. The described synthetic approach mirrors that of a cyclophane previously reported by the Bodwell group, but makes use of cyclohexanone instead of cyclopentanone in the initial IEDDA-based multicomponent reaction. The synthesis was brought to the final step, but none of the target pyrenophane was obtained from the key McMurry/VID reaction.

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List of Abbreviations

Calc.	calculated
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzophenone
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethylsulfoxide
d	doublet
EDG	electron-donating group
EWG	electron-withdrawing group
equiv.	equivalent
FMO	frontier molecular orbital
h	hour(s)
<i>J</i>	coupling constant
HOMO	highest occupied molecular orbital
HRMS	high resolution mass spectrometry
HWE	Horner-Wadsworth-Emmons
Hz	hertz
IEDDA	inverse electron demand Diels-Alder
LUMO	lowest unoccupied molecular orbital
M ⁺	molecular ion peak
m	multiplet
min.	minute(s)
mol	moles(s)
mp	melting point

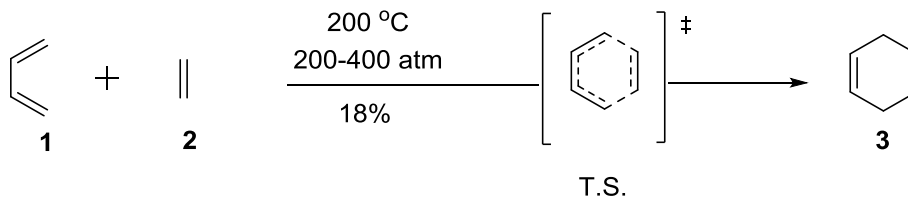
MO	molecular orbital
NMR	nuclear magnetic resonance (spectroscopy)
Ph	phenyl
ppm	parts per million
quint	quintet
t	triplet
rt	room temperature
THF	tetrahydrofuran
tlc	thin layer chromatography
TMS	trimethylsilyl
s	singlet

1. Introduction

1.1 Diels-Alder Reaction

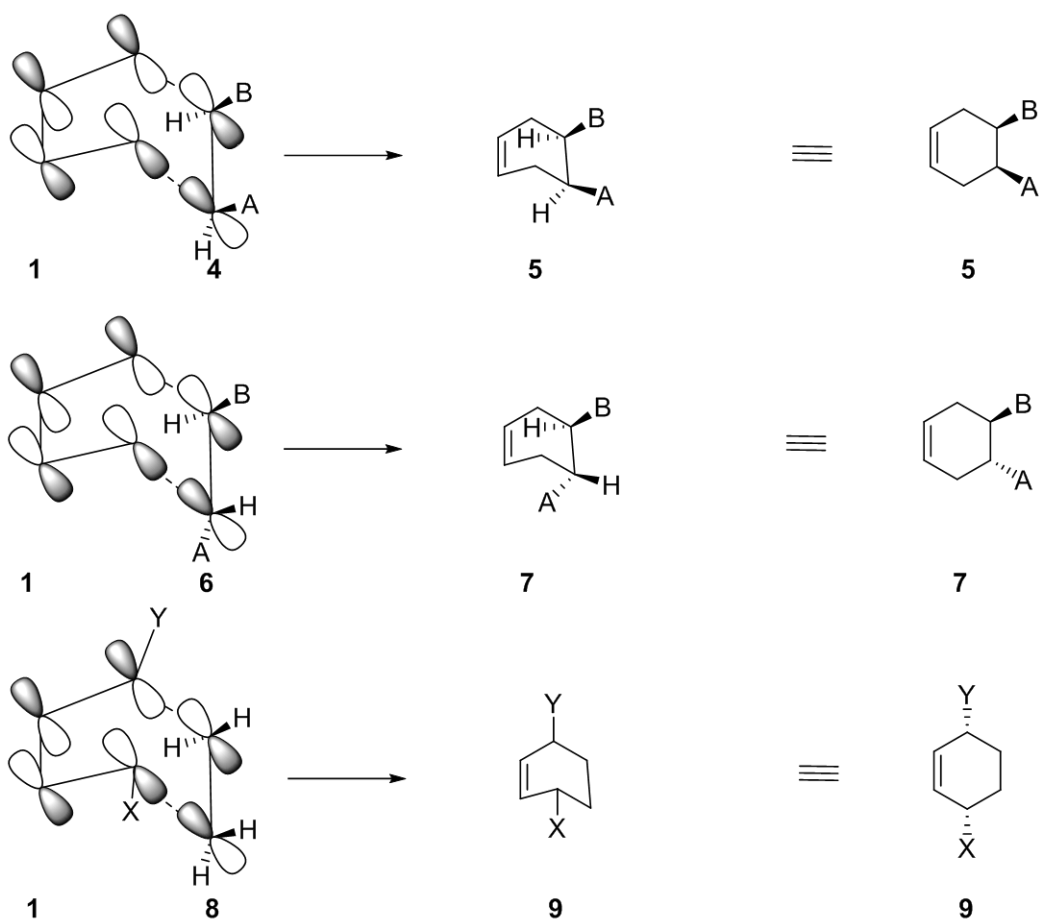
The Diels-Alder reaction is one of the most extensively used reactions in organic synthesis. Otto Paul Hermann Diels and his student Kurt Alder were the pioneering investigators of this reaction. Starting in 1928 they reported the formation of several adducts from the reactions of various 1,3-dienes with various alkenes and published a series of papers about this transformation.^{1,2,3} The versatility and applicability of the Diels-Alder reaction in synthetic organic chemistry was recognized by the award of the 1950 Nobel Prize in chemistry to Diels and Alder.

In the parent Diels-Alder reaction, 1,3-butadiene (**1**) (the diene, or the 4π electron component) reacts with ethene (**2**) (the dienophile, or 2π electron component) to afford cyclohexene (**3**) (the adduct) (Scheme 1.1).⁴ From a basic perspective, it can be viewed as both a 1,4-addition of ethene to 1,3-butadiene and a 1,2-addition of 1,3-butadiene to ethene.



Scheme 1.1 The parent Diels-Alder cycloaddition reaction.

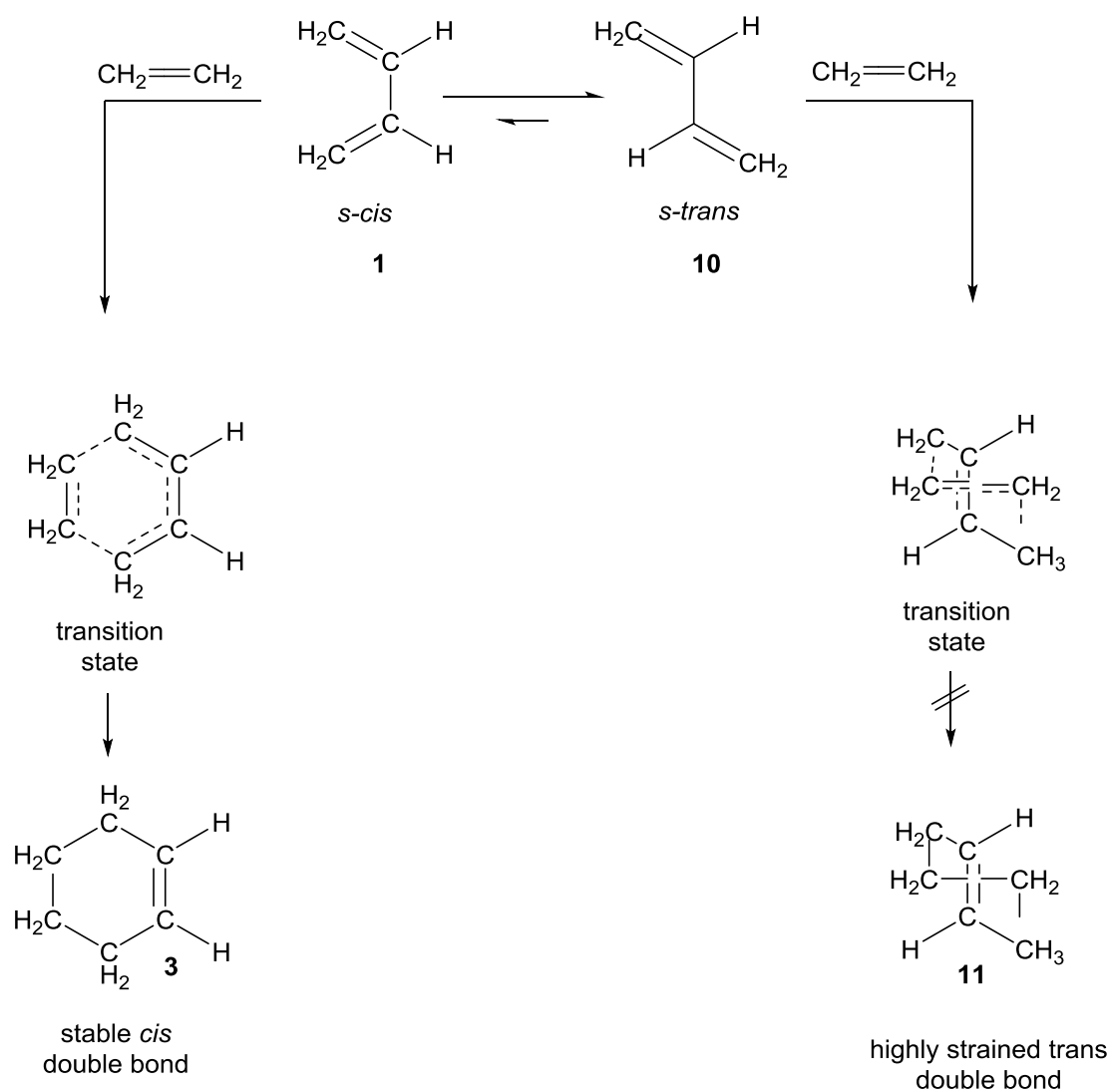
The Diels-Alder reaction belongs to a large class of reactions called pericyclic reactions, i.e. those that are concerted and proceed through a cyclic transition state. For both components of the reaction, bond formation occurs through the overlap of π orbital lobes that are on the same face of the π system, i.e. in a suprafacial fashion (Scheme 1.2). As such, the Diels-Alder reaction is formally described as a $[4\pi_s + 2\pi_s]$ cycloadduct. Woodward and Hoffmann have defined suprafacial addition as “the addition of lobes on the same side of the π system”.⁵



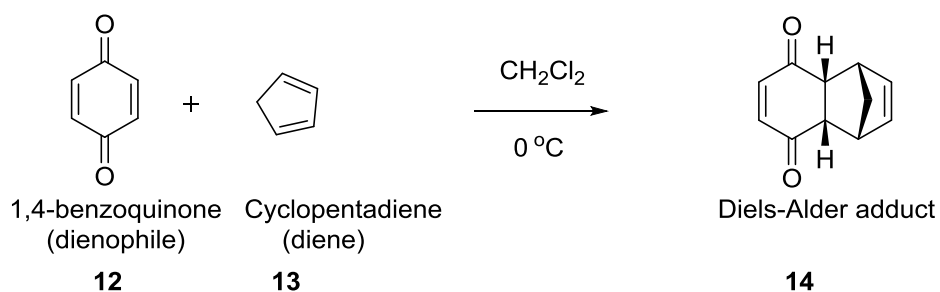
Scheme 1.2 Suprafacial addition and conservation of relative stereochemistry of the diene and the dienophile in the cycloadduct.

A key consequence of the concerted nature (Scheme 1.2) of the Diels-Alder is that it is stereospecific. In other words, stereochemical relationships in the diene and/or dienophile are retained in the adduct. More specifically, a *cis*-configured dienophile **4** will react with diene **1** to afford a *cis*-4,5-disubstituted cyclohexene **5**. Similarly, a *trans*-configured dienophile **6** gives rise to a *trans*-4,5-disubstituted cyclohexene **7**. Along the same lines, 1,4-disubstituted diene **8** leads to the formation of *cis*-3,6-disubstituted cyclohexene **9**.

For a Diels-Alder reaction to occur, the diene must adopt an *s-cis* conformation. In fact, one of the more important contributors to the Diels-Alder reactivity of a diene is how difficult it is for it to adopt the *s-cis* conformation. For acyclic dienes, the *s-cis* conformer is less favorable than the corresponding *s-trans* conformer (Scheme 1.3).⁶ Even if the *s-cis* conformer is very sparsely populated, the Diels-Alder reaction can still occur, albeit slowly. Diels-Alder reaction through the *s-trans* conformer is allowed from a molecular orbital perspective, but the product is a very highly strained *trans*-cyclohexene. Thus, a very high level of molecular distortion would need to occur to reach the transition state and the reverse reaction would be highly exergonic. Because of an enforced *s-cis* conformation, cyclic dienes usually react considerably faster than acyclic dienes.⁷ (Scheme 1.4)

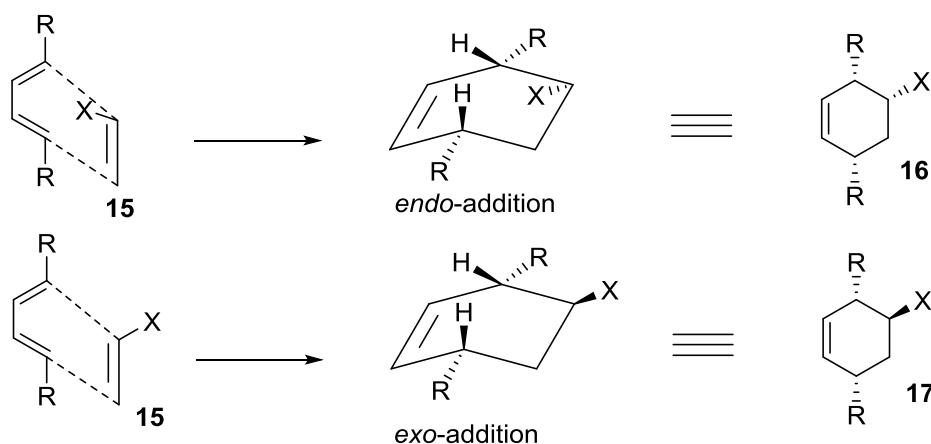


Scheme 1.3 The *s-cis* and *s-trans* transition states.



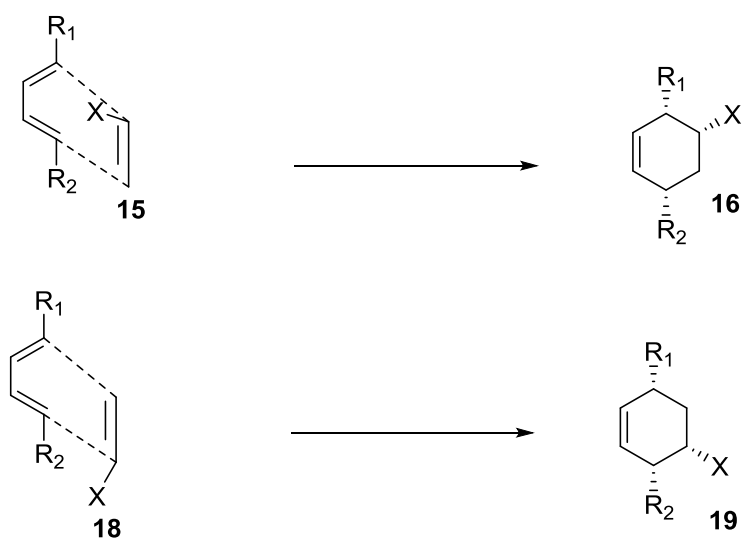
Scheme 1.4 Reaction of cyclic diene.

Another stereochemical feature of the Diels-Alder reaction is *endo/exo* selectivity. This has to do with the arrangement of the substituents in the dienophile with respect to the diene in the transition state. When the substituent of a monosubstituted diene is toward the π system of the diene the term “*endo*” is used to describe the transition state and often the product arising from it. On the other hand, when the substituent is situated away from the π (π) system the term “*exo*” is used. The two different products (**16** & **17**) are diastereomers. The adduct that results from the *endo* transition state is usually the major product and this is known as the “Alder rule.”⁸



Scheme 1.5 The “*endo*” and the “*exo*” transition states.

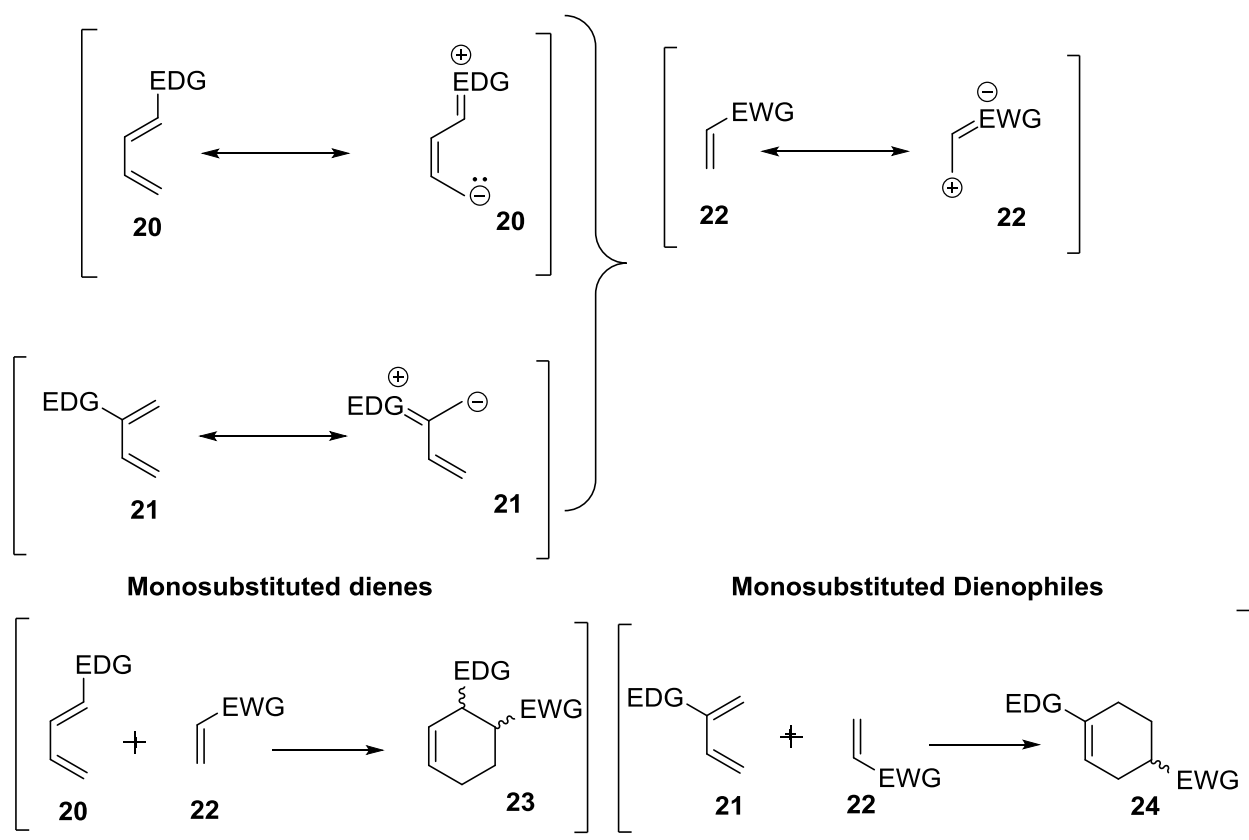
The examples in the Scheme 1.5 involve a symmetrically substituted diene and a mono-substituted dienophile. When an unsymmetrically substituted diene reacts with the same monosubstituted dienophile through an *endo* transition state, two regioisomeric products can form depending upon which way around the dienophile is oriented with respect to the diene. (Scheme 1.6)



Scheme 1.6 Possible regiochemical outcomes of the Diels-Alder reaction when R_1 is not equal to R_2 .

The consideration of resonance is a simple, but quite effective way to predict the regiochemical outcome of Diels-Alder reactions (Scheme 1.7). The alignment of sites of partial negative and partial positive charge on the diene and dienophile usually leads to a correct prediction of the regiochemical result.

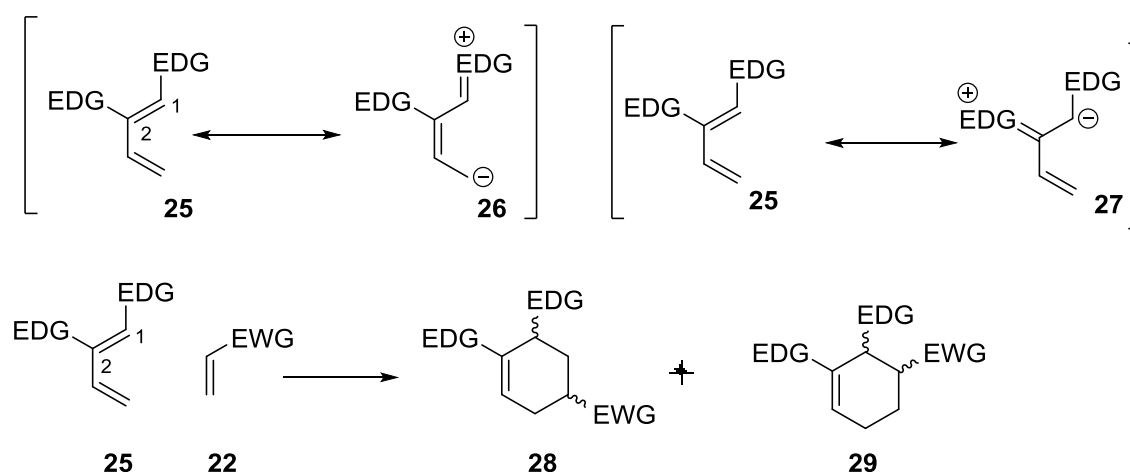
A diene (**20**) with an electron donating group at the 1 position would be expected to react with a mono-substituted electron deficient dienophile (**22**) to afford a 3,4-disubstituted cyclohexene (**23**) ("*pseudo-ortho*" product), whereas a 2-substituted diene (**21**) would be expected to favour a 1,4-disubstituted alkene (**24**) ("*pseudo-para*" product).



Scheme 1.7 Valence bond explanation of the regiochemical outcome of the Diels-Alder reaction with monosubstituted dienes.

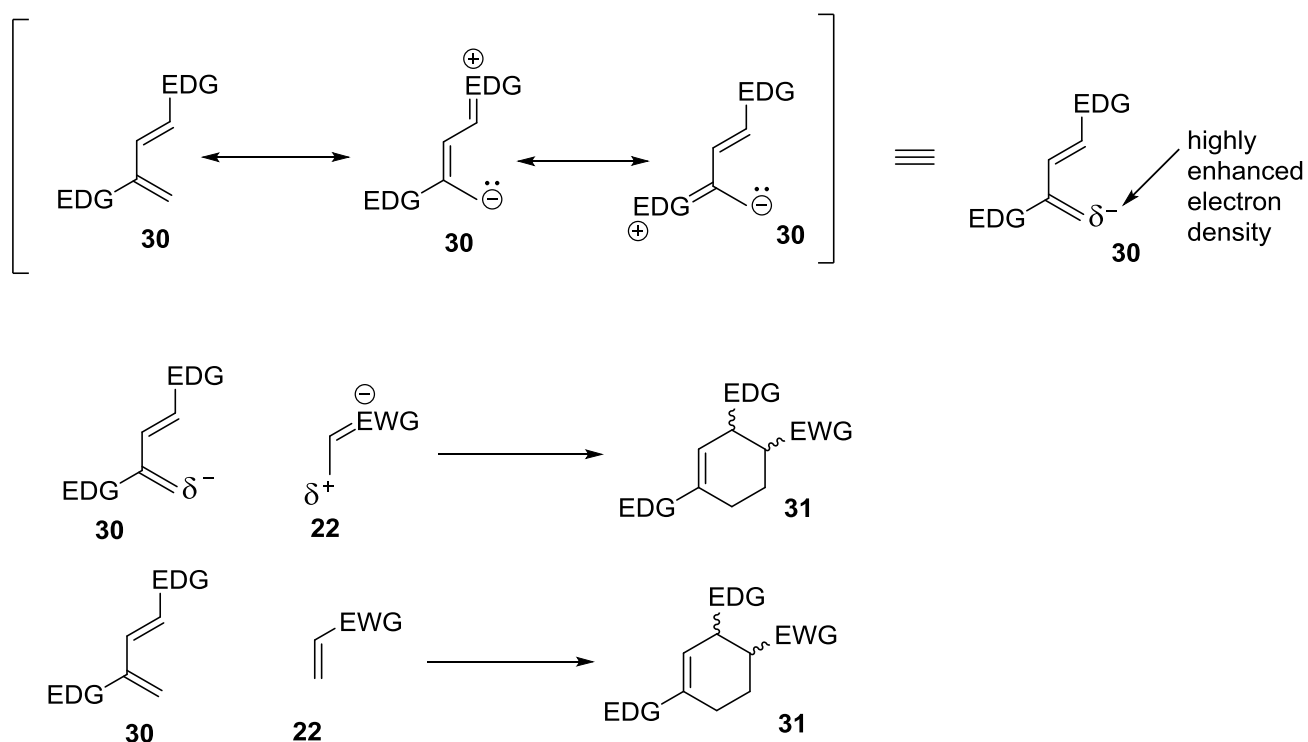
The situation becomes more complicated when the diene bears more than one substituent. Depending on the substitution pattern of the diene, the substituents can either

work against one another or work co-operatively to direct the regiochemistry. For a 1,2-disubstituted diene, one of the electron-donating groups increases electron density at one end of the diene and the other one increases the electron density at other end (Scheme 1.8). This can result in low regioselectivity.



Scheme 1.8 Valence bond explanation of the regiochemical outcome of the Diels-Alder reaction with a disubstituted diene at positions 1 and 2.

A more interesting case is when electron-donating groups are placed at the 1 and 3 positions of the diene. Both substituents donate electron density to the same terminal carbon atom as in diene (**30**) (Scheme 1.9). The result of this is very high regiochemical control in reactions with an electronically biased dienophile (**22**). Furthermore Diels-Alder reactions of such dienes are known to proceed rapidly.



Scheme 1.9 Resonance consideration of the Diels-Alder reaction

Some of the most widely used and reliable dienes like Danishefsky's diene **32**, Brassard's diene **33** and Rawal's diene **34** (Figure 1.1),^{9,10,11} have electron-donating groups at both the 1 and 3 positions of the diene unit and such dienes react with high regioselectivity.

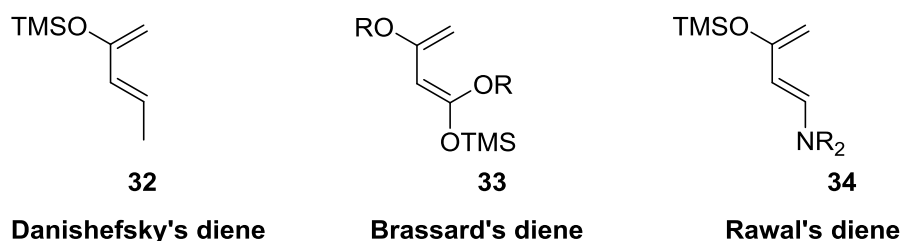
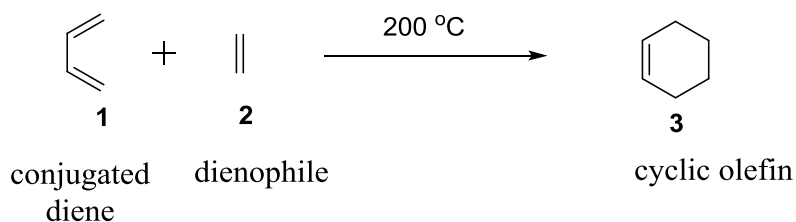


Figure 1.1 Some dienes bearing electron donating groups at 1 and 3 positions that reacts with high regioselectivity.

The preceding discussion has dealt with electron-rich dienes and electron-deficient dienophiles, but this is just one of the three different electronic types of Diels-Alder reaction. As discussed below, this classification is based on the presence or absence of the electronic nature of the two reaction components, which corresponds to electron-donating groups or the electron-withdrawing groups on the dienes and dienophiles. More formally, the three types of Diels-Alder reactions can be categorized according to the type of frontier molecular orbitals (FMO) interactions that are dominant as the cycloaddition takes place. In fact, the energy differences between the HOMO of one component and the LUMO of the other component determine which type of Diels-Alder reaction takes place.

The parent Diels-Alder reaction (between 1,3-butadiene **1** and ethylene **2**) can be represented by the molecular orbital energy level diagram shown in Figure 1.2. The $\text{HOMO}_{\text{diene}} - \text{LUMO}_{\text{dienophile}}$ and the $\text{HOMO}_{\text{dienophile}} - \text{LUMO}_{\text{diene}}$ energy differences are about equal and quite large. Reactions of this type are referred to as neutral Diels-Alder reactions, since the extent of orbital interaction is inversely proportional to energy differences, meaning neither interaction will be dominant and the rate of this Diels-Alder reaction will be slow (Scheme 1.10)

As introduced earlier, the parent Diels-Alder reaction requires very forcing conditions. The same is true for reactions in which the diene and/or the dienophile have/has electronically neutral substituents. For reasons that will become clear shortly, the same is true for reaction partners that are both electron rich and both electron deficient.



Scheme 1.10 Neutral Diels-Alder reaction.

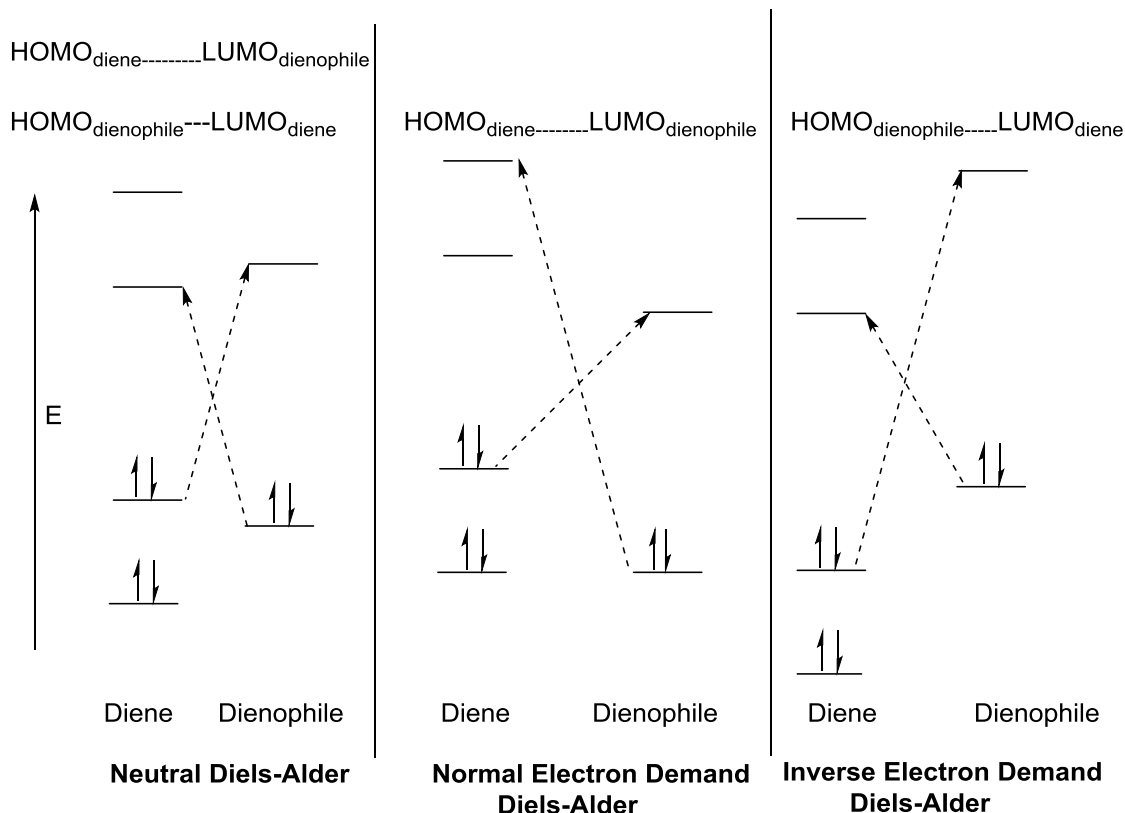
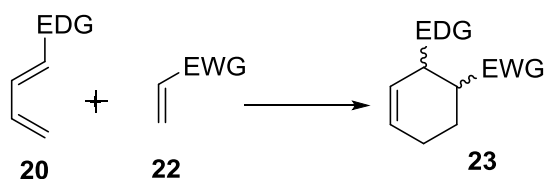


Figure 1.2 Molecular orbital description of the varying types of Diels-Alder reaction.

1.2 Normal Diels-Alder reaction

The normal Diels-Alder reaction takes place when electron-donating substituents are present on the diene and electron-withdrawing substituents reside on the dienophile. Attachment of an electron donating group results in the raising of the energy of its frontier molecular orbitals, whereas the presence of an electron-withdrawing group on the dienophile has the effect of lowering the energies of its frontier molecular orbitals (FMOs). These complementary changes to the FMOs of the reacting species cause the $\text{HOMO}_{\text{diene}} - \text{LUMO}_{\text{dienophile}}$ energy gap to decrease and the $\text{HOMO}_{\text{dienophile}} - \text{LUMO}_{\text{diene}}$ energy gap to increase relative to the parent system. The reduction in the $\text{HOMO}_{\text{diene}} - \text{LUMO}_{\text{dienophile}}$ energy barrier results in an increase in the rate of reaction, which permits the normal Diels-Alder reaction to be carried out under far milder conditions than the neutral Diels-Alder reaction (Scheme 1.11). Most Diels-Alder reactions fall under this category and this is why it is described as "normal".



Scheme 1.11 Normal electron demand Diels-Alder reaction

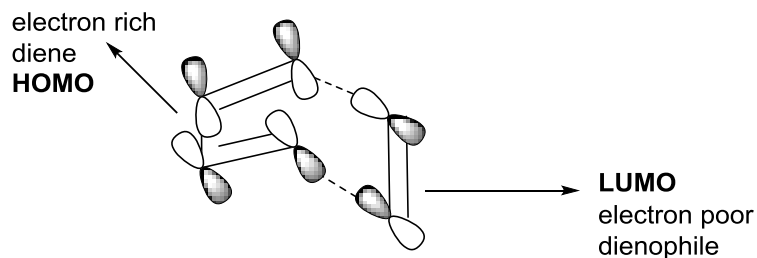


Figure 1.3 Molecular orbital description of the normal electron demand Diels-Alder reaction.

1.3 Inverse electron demand Diels-Alder reaction (IEDDA)

The IEDDA reaction occurs when electron withdrawing groups are attached to the diene and electron donating groups are attached to the dienophile. Similar to the normal Diels-Alder reaction, the complimentary electron rich/electron poor pairing of the reaction partners has the effect of lowering one of the HOMO-LUMO energy differences relative to the neutral reaction. Specifically, the $\text{HOMO}_{\text{dienophile}} - \text{LUMO}_{\text{diene}}$ interaction is the dominant one in the IEDDA reaction. As with the normal Diels-Alder reaction, appropriate substituted dienes and dienophiles can undergo Diels-Alder reactions under mild conditions (Scheme 1.12).



Scheme 1.12 Inverse electron demand Diels-Alder reaction (IEDDA).

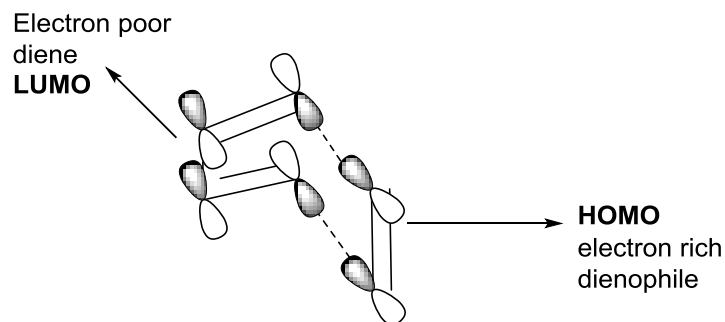
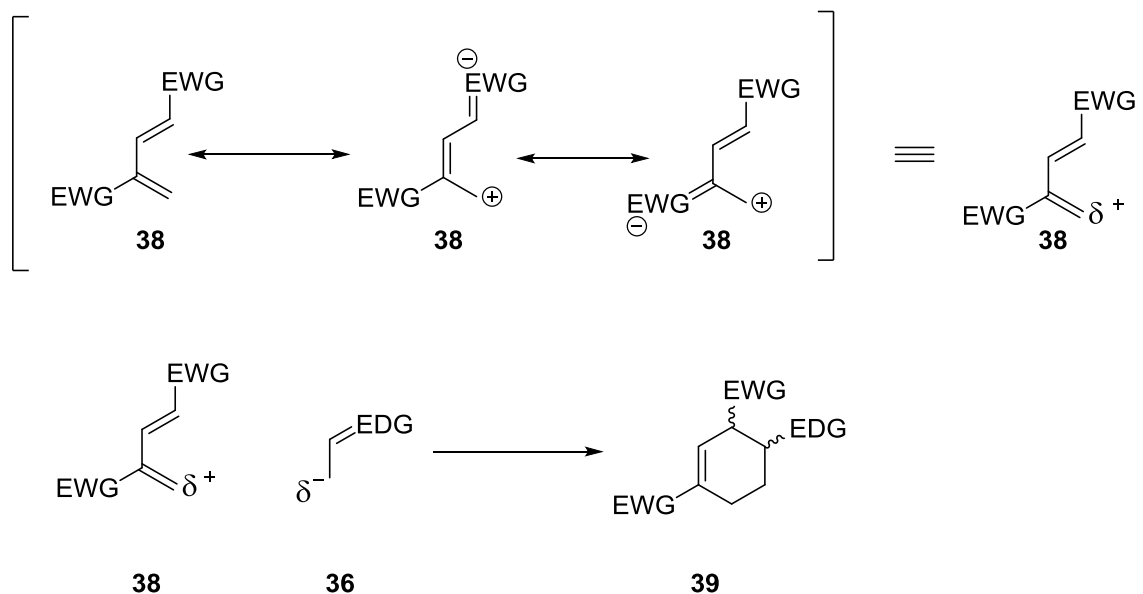


Figure 1.4 Molecular orbital description of the IEDDA reaction.

As stated earlier, electron rich dienes bearing electron-donating groups at the 1 and 3 positions such as Danishefsky's diene **32** and Rawal's diene **34** have enjoyed widespread use in the synthesis of natural products because of their high reactivity and regioselectivity.¹² Dienes that are electronically complementary to Danishefsky's and Rawal's dienes, i.e. those that have electron withdrawing groups at the 1 and 3 positions, would also be expected to exhibit high reactivity and predictable regiochemistry in the IEDDA reactions. Similar to the normal Diels-Alder reaction, the net effect of having electron-withdrawing groups at the 1 and 3 positions is that they work co-operatively to electronically bias the diene (Scheme 1.13). As a result, an electronically rich and biased dienophile, e.g., dienophile **36**, will react with its counterpart diene in a regioselective manner.



Scheme 1.13 Resonance consideration of the IEDDA reaction.

1.4 Dienes

Dienes bearing electron-withdrawing groups in the 1 and 3 positions were identified as potentially reactive and regioselective dienes for studies of the IEDDA reaction in the Bodwell group. Simple electron-deficient dienes bearing electron-withdrawing groups at 1 and 3 positions had been reported previously and had been found to polymerize, presumably as a consequence of the very low-lying LUMOs. For example, the synthesis and easy polymerization (in a 1,4-fashion) of dienes **40-43**, was reported in 1981 by Hall and Ahn.¹³

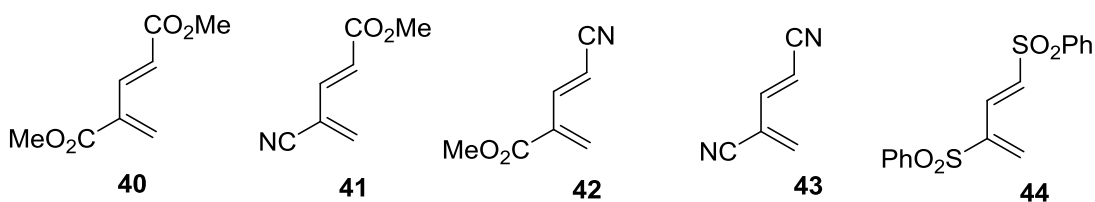
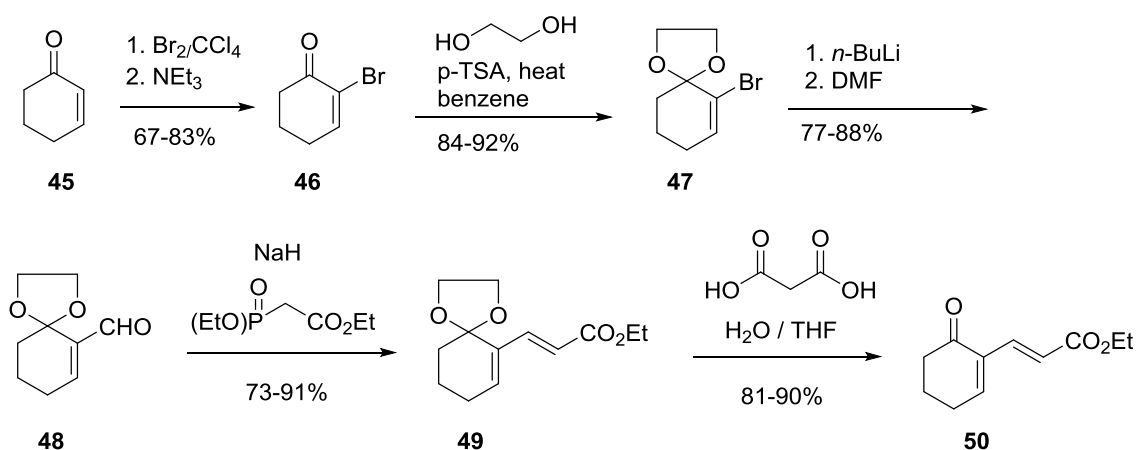


Figure 1.5 Simple electron deficient dienes.

Diene **44** was also found to undergo same IEDDA reactions when generated *in situ*, but polymerized in its pure form. To combat the issue of polymerization of the simple electron deficient dienes, the Bodwell group turned their attention towards the synthesis of more heavily substituted or annulated systems. The expectation was that this would stabilize these dienes (kinetically and thermodynamically) and thus discourage polymerization.

Cycloalkane-annulated dienes were investigated first. The first report of cycloalkene-annulated diene **50** in the group was reported by Pi and Bodwell (Scheme 1.14)¹⁴ in 1997. Cyclohexenone **45** was subjected to a bromination/dehydrogenation sequence to give bromoketone **46**. Immediate protection of the ketone as a cyclic acetal yielded **47**. A halogen-metal exchange was performed by treatment of **47** with *n*-butyllithium, and this was followed by the addition of DMF to give aldehyde **48**. Horner-Wadsworth-Emmons (HWE)¹⁵ reaction of **48** with a phosphorus ylide yielded diene **49**. Removal of the protecting group afforded electron-deficient diene **50**.



Scheme 1.14 Synthesis of cycloalkene annulated diene **50**.

Using the general approach in Scheme 1.14, other electron-deficient dienes **51-53** (Figure 1.6) were also synthesized by the group. Dienes **51-53** were found to be stable enough to be isolated and purified using standard techniques, but self-reacted in an unidentified way when stored at room temperature. Storage at $-20\text{ }^{\circ}\text{C}$ under nitrogen extended the shelf life to several weeks, but it was found to be most convenient to build stockpiles of the much more stable diene **49** and generate fresh **50** as needed.

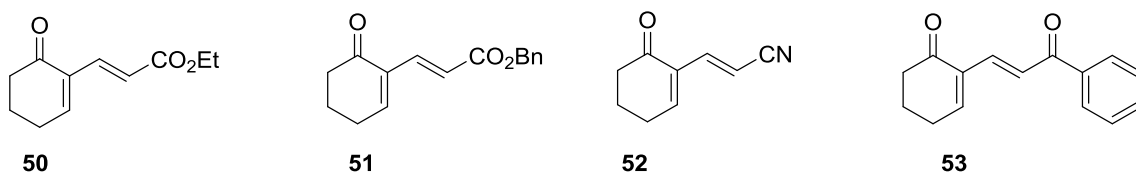
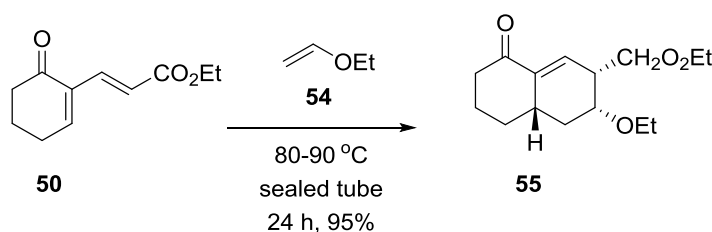


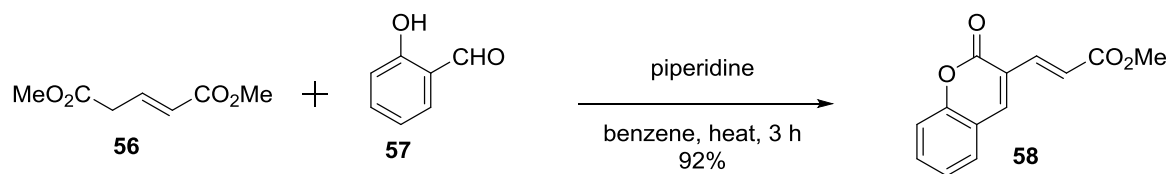
Figure 1.6 Other cycloalkene annulated dienes synthesized using HWE reaction.

Dienes **50-53** reacted with a variety of electron rich dienophiles to give IEDDA adducts (Scheme 1.15). In all cases, nothing less than complete regioselectivity was observed. For example, diene **50** reacted with ethyl vinyl ether (**54**) to afford adduct **55** as a single diastereomer. In addition to the complete regioselectivity, the reaction proceeded with complete *endo*-selectivity.

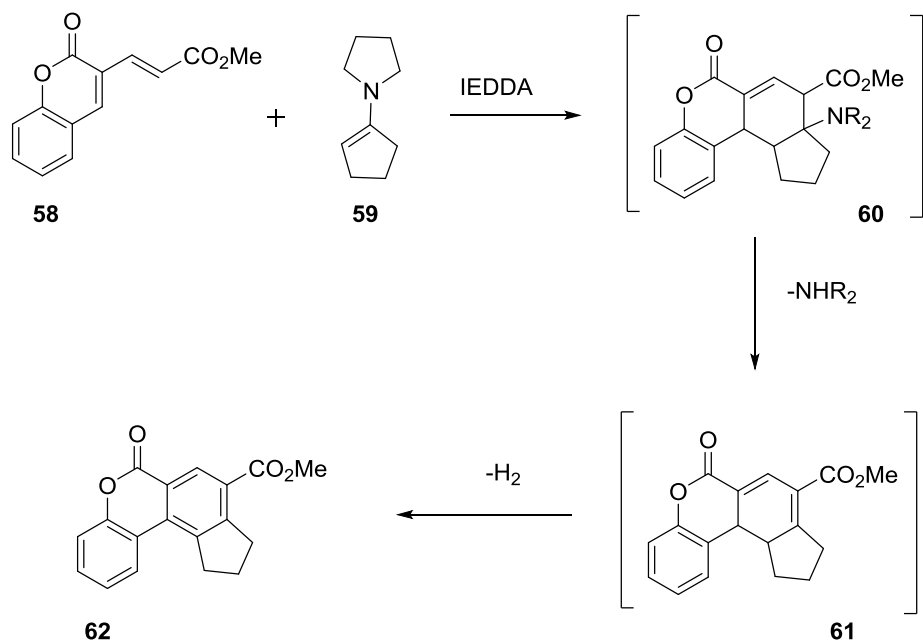


Scheme 1.15 Reaction of diene **50** with dienophile **54** to give an IEDDA adduct

The synthesis of coumarin-fused diene **58** was reported later by the group in 1999 (Scheme 1.16)¹⁶ in only one synthetic operation from salicylaldehyde **57** and dimethyl glutaconate **56**. Diene **58** was found to be more stable than dienes **50-53**, and can be exposed to air for years without change. The increased stability comes with lower reactivity. However, the use of stronger dienophiles, like enamines, gave rise to IEDDA reactivity. In most cases, IEDDA adducts were not observed. Aromatized products arose from subsequent reactions. For example, reaction of **58** with enamine **59** presumably afforded adduct **60**, which underwent 1,2-elimination of pyrrolidine and dehydrogenation to afford dibenzo[b,d]-6H-pyran-6-one **62**. Subsequently, it was found that the dienophile (enamine) could be formed *in situ*. Again, complete regioselectivity was always observed.

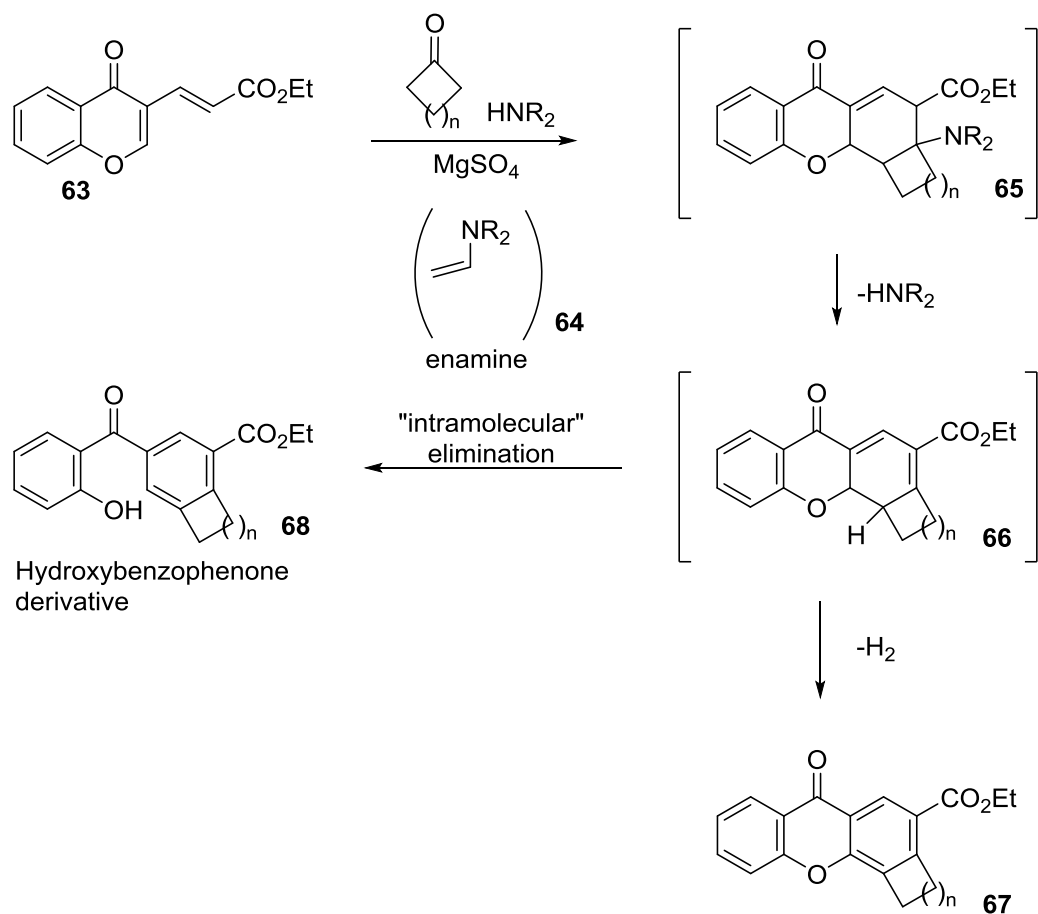


Scheme 1.16 Synthesis of coumarin-fused diene **58**.



Scheme 1.17 Mechanism for the synthesis of aromatized product.

Chromone-fused diene **63** (a constitutional isomer of **58**) was then identified as a potentially more useful diene for IEDDA reactions leading to aromatic products via a similar domino process (Scheme 1.18).



Scheme 1.18 Synthesis of hydroxybenzophenones.

In fact, diene **63** was found to react as expected with enamines to give rise to an IEDDA adduct **65**, which could undergo 1,2-elimination of HNR_2 to afford dihydroxanthone **66**. Instead of undergoing the dehydrogenation to give **67**, an

"intramolecular elimination" took place to give 2-hydroxybenzophenone **68**. The presence of an excellent internal leaving group (stabilized phenoxide) situated beta to relatively acidic hydrogen atom is likely why the new aromatic ring was formed in this fashion rather than dehydrogenation (Scheme 1.18).¹⁷

A series of other dienes **63**, **69**, and **70** was synthesized, but only preliminary work was done on them. The main objective of this work is to carry out more in-depth studies on the IEDDA reactivity of the chromone-fused dienes **63**, **69** and **70** (Figure 1.7).

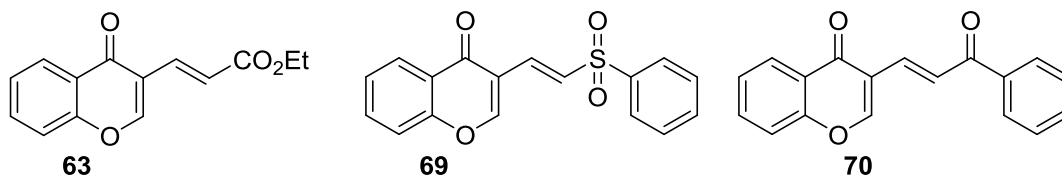


Figure 1.7 Electron deficient dienes used in synthesis.

1.5 References

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Chapter 2

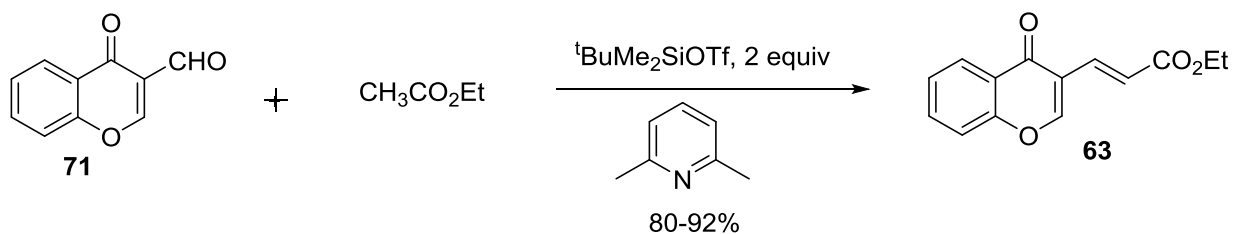
2.1 Introduction

One of the major aims of this project was the investigation of the IEDDA chemistry of the related dienes **63**, **69**, and **70** (Figure 1.7, Page 22). To achieve this aim, the first objective was to synthesize the dienes.

2.2 Results and Discussion

2.2.1 Synthesis of chromone-fused diene **63**

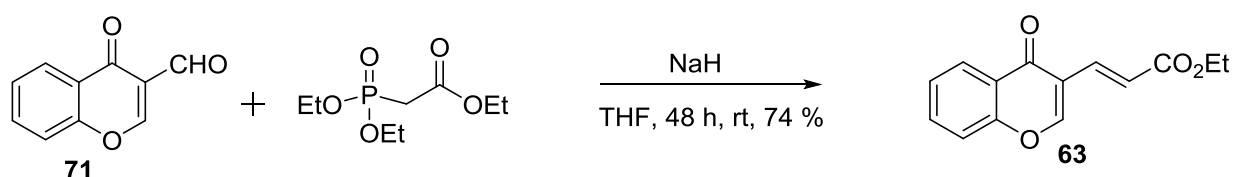
Diene **63** was first synthesized by Akiba *et al.* (Scheme 2.1).¹ Their Synthesis involved the aldol condensation of 3-formylchromone **71** with ethyl acetate in the presence of TBSOTf and 2,6-lutidine. The reaction progressed in high yield giving rise to **63** in one synthetic operation.



Scheme 2.1 Synthesis of a chromone-fused electron deficient diene by Akiba *et al.*¹

A later report from the Bodwell group showed that diene **63** can also be synthesized using the Horner-Wadsworth-Emmons (HWE) modification of the Wittig reaction.²⁻⁴ The HWE reaction typically affords only the *E*-isomer of the newly formed alkene when a stabilized ylide is used, i.e. an ylide bearing an anion-stabilizing group like

the ylide derived from triethyl phosphonoacetate. The HWE reaction approach was chosen to gain access to diene **63**. Thus, commercially available 3-formylchromone **71** was reacted with the ylide derived from triethyl phosphonoacetate to afford diene **63** in 74% yield. As expected, only the *E*-isomer was formed, as was evident through the large coupling constant ($J = 15.1$ Hz) between the two protons attached to the newly formed alkene.



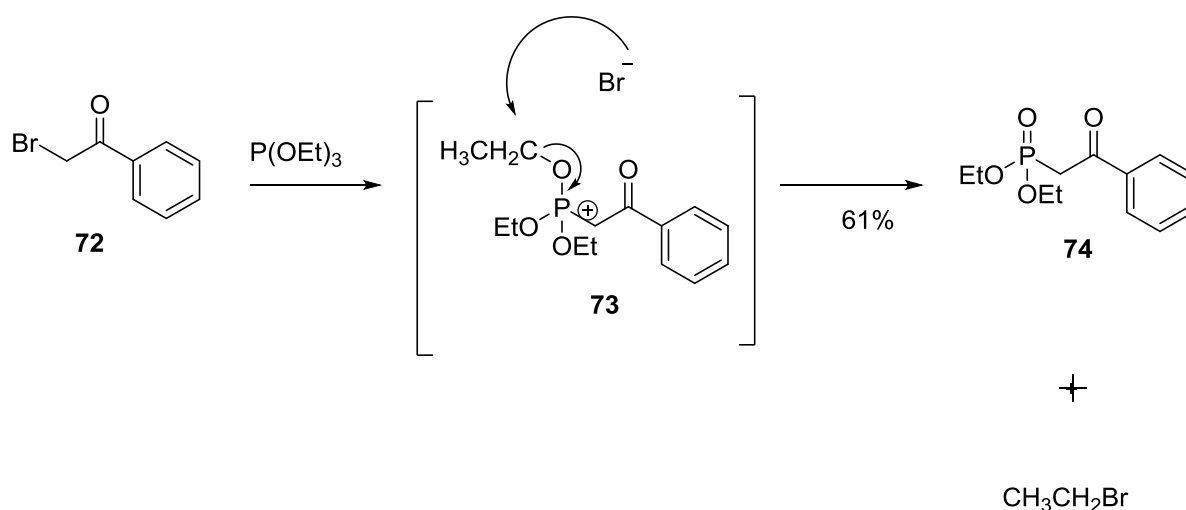
Scheme 2.2 Synthesis of a chromone-fused electron-deficient diene by the Bodwell group.

In contrast to the previously reported procedure, in which diene **63** was isolated by column chromatography, it was found that it could be obtained in pure form through crystallization of the crude product from absolute ethanol. The 74% yield is slightly better than that obtained using column chromatography (69%).¹⁷

2.2.2 Synthesis of phenyl ketone substituted diene **70**

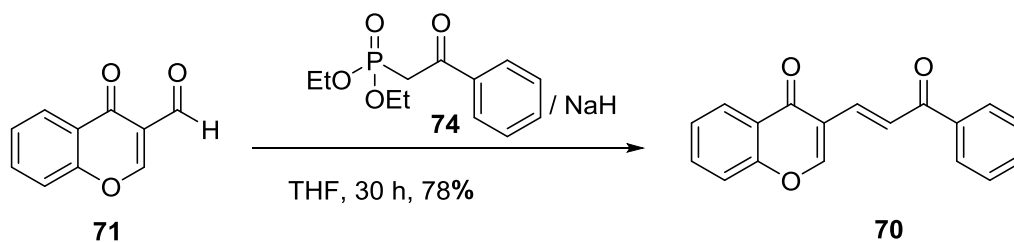
Diene **70** was also synthesized using the HWE methodology according to a previously reported procedure in the Bodwell group. In this case, the synthesis involves two synthetic steps. The first step was the generation of phosphonate **74**, which was obtained from the reaction of commercially available 2-bromoacetophenone **72** with triethylphosphite. The first step is an $\text{S}_{\text{N}}2$ reaction to afford intermediate **73**. The bromide

ion plays a dual function in the reaction pathway. The bromide ion first serves as a good leaving group that facilitates the attack by the phosphorus lone pair of triethylphosphite. The bromide ion then reacts with intermediate **73** via an Arbuzov dealkylation reaction to afford phosphonate **74** and ethyl bromide. The low boiling point (37 °C – 40 °C) of ethyl bromide means that it could be removed from the reaction mixture through distillation. (Scheme 2.3)²



Scheme 2.3 Synthesis of phenyl ketone phosphonate

Using HWE reaction conditions,⁶ the carbanion generated by the reaction of phenyl ketone phosphonate **74** with NaH was reacted with 3-formylchromone **71** to afford the diene **70** (Scheme 2.4).² The previously reported process called for a reaction of 24 h, but it was found by (tlc analysis) that some 3-formylchromone remained after this time. Extending the reaction time to 30 h resulted in the complete consumption of 3-formylchromone, and diene **70** was isolated in 78% yield. This represents a slight improvement over the previously reported yield of 70%.

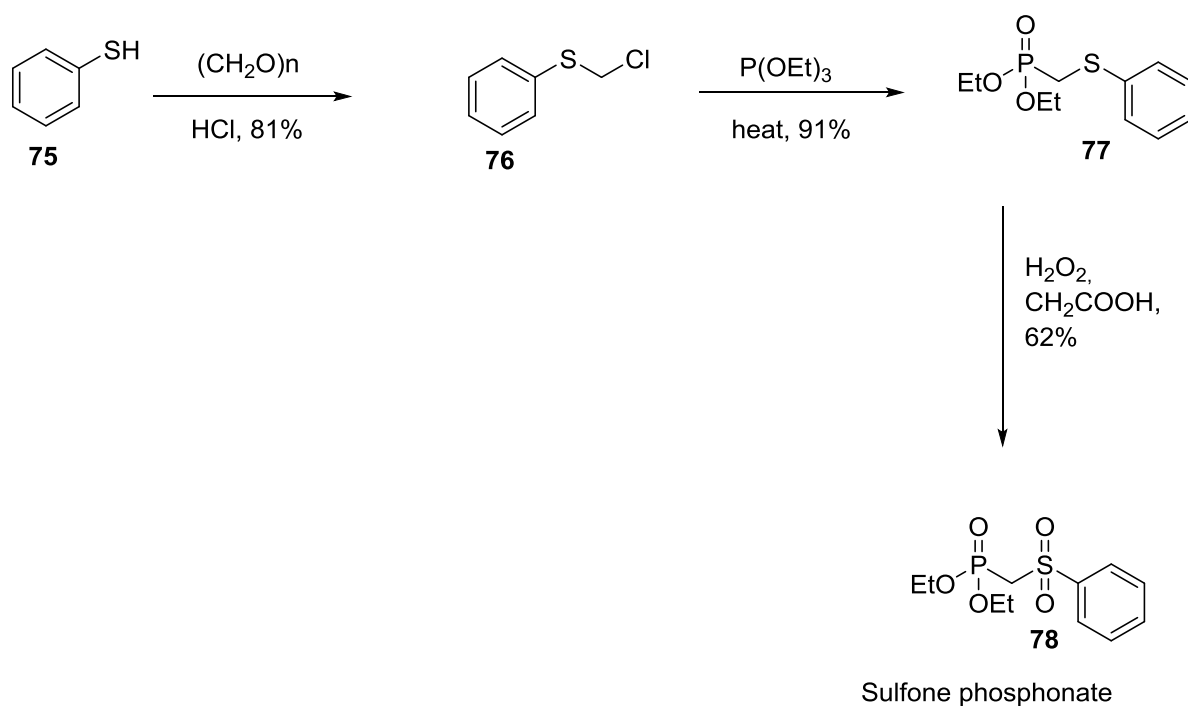


Scheme 2.4 Synthesis of diene **70**.

Similar to the synthesis of diene **63**, only the *E*-isomer of the newly formed double bond was formed as this was clearly evident through large coupling constant of 15.1 Hz between the two vinyl protons. Column chromatography afforded diene **70** in 78%, which is slightly better than the previously reported yield of (70%).^{2,5,17}

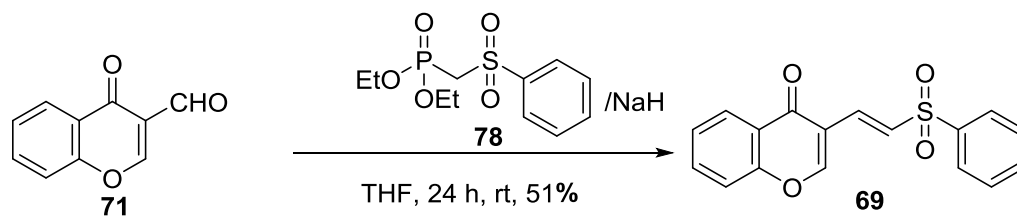
2.2.3 Synthesis of sulfone substituted diene **69**

A stockpile of diene **69** was made available by the previous Bodwell group members. Reporting on the synthesis of diene **69** by the Bodwell group,² the synthesis of diene **69** was also accomplished employing the HWE reaction methodology. The synthesis of the required phosphonate **78** consisted of a 3-step sequence (Scheme 2.5).²



Scheme 2.5 Synthesis of sulfone phosphonate **78**.

Commercially available benzenethiol **75** acted as the starting material and was reacted with paraformaldehyde in the presence of concentrated hydrochloric acid to give chloromethyl phenyl sulfide **76**, which was then reacted with triethylphosphite at reflux to bring about an Arbuzov reaction to give phosphonate **77**. This was then oxidized with $\text{H}_2\text{O}_2/\text{HOAc}$ to afford the desired sulfone phosphonate **78**

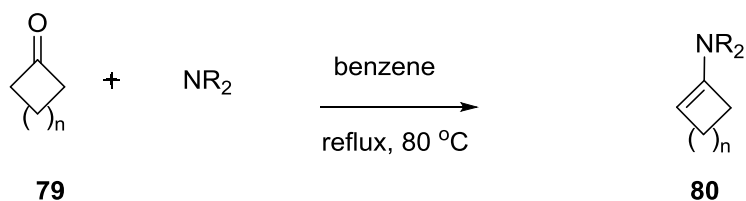


Scheme 2.6 Synthesis of sulfone diene **69**.

To complete the synthesis of diene **69**, the ylide derived from phosphonate **78** was reacted with 3-formylchromone **71** to afford diene **69** (Scheme 2.6)^{2, 5} Similar to the other dienes within the scope of this work, only the *E*-isomer of this diene was formed, which was evident from large coupling constant of 15.0 Hz between the protons of the newly formed double bond.

2.3 Dienophiles for IEDDA reaction

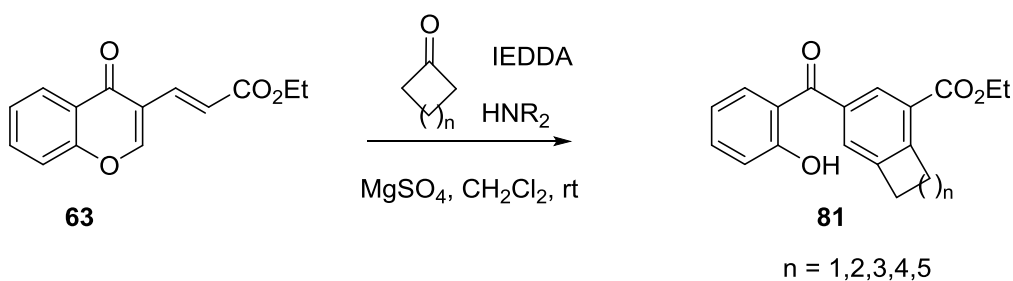
Enamines derived from cycloalkanones were used as dienophiles for IEDDA reactions with the chromone-fused dienes. Generally, enamines are known to be among the more reactive electron rich dienophiles. Previous work in the Bodwell group showed that enamines derived from cycloalkanones are good candidates for the investigation of this IEDDA reaction with the dienes under consideration.^{7,17} Enamines for these reactions can be synthesized (preformed) prior to reaction with the diene preformed, or they can also be synthesized *in situ* during the course of the domino reactions. The standard procedure for generating these enamines preformed is to reflux the ketone or cycloalkanone and an appropriate secondary amine in benzene with azeotropic removal of water (Scheme 2.7).



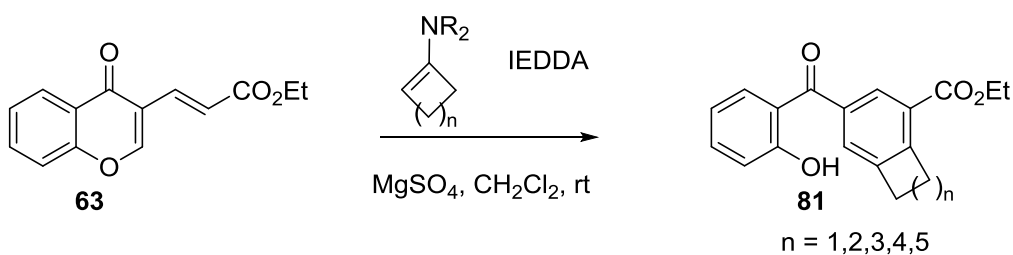
Scheme 2.7 Synthesis of enamines. n = 1,2,3,4

Enamines can also be synthesized *in situ* in the course of the IEDDA reaction by adding the enamine precursors (secondary amine and ketone) to the reaction mixture. Water is liberated in the process of enamine formation, so a drying agent can be added such that water does not retard the reaction. Generating the enamine *in situ* offers a great advantage of saving time, resources and effort. Furthermore, the formation and/or isolation of enamines derived from certain ketones can be difficult.

The IEDDA reaction for the synthesis of hydroxybenzophenones can be conducted using any of the two methods above. Carrying out this reaction using the initially reported *in situ* method of synthesis involves using the conditions shown in Scheme 2.8(a) with pyrrolidine as the secondary amine and dichloromethane as the solvent. The preformed method also involves adding the preformed enamine to a stirred solution of the diene and dichloromethane at room temperature (Scheme 2.7(b)).



Scheme 2.8(a) Hydroxybenzophenone synthesis using the *in situ* method.

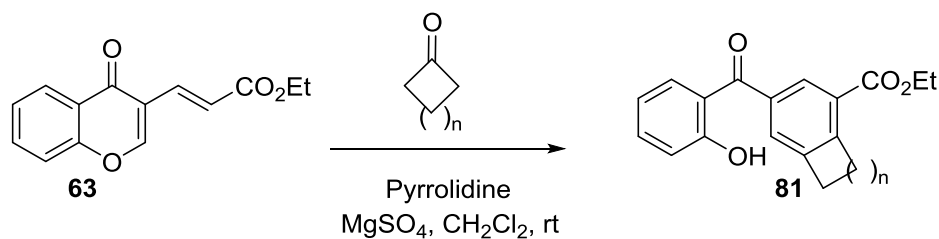


Scheme 2.8(b) Hydroxybenzophenone synthesis using the preformed method.

2.4 Reaction optimization

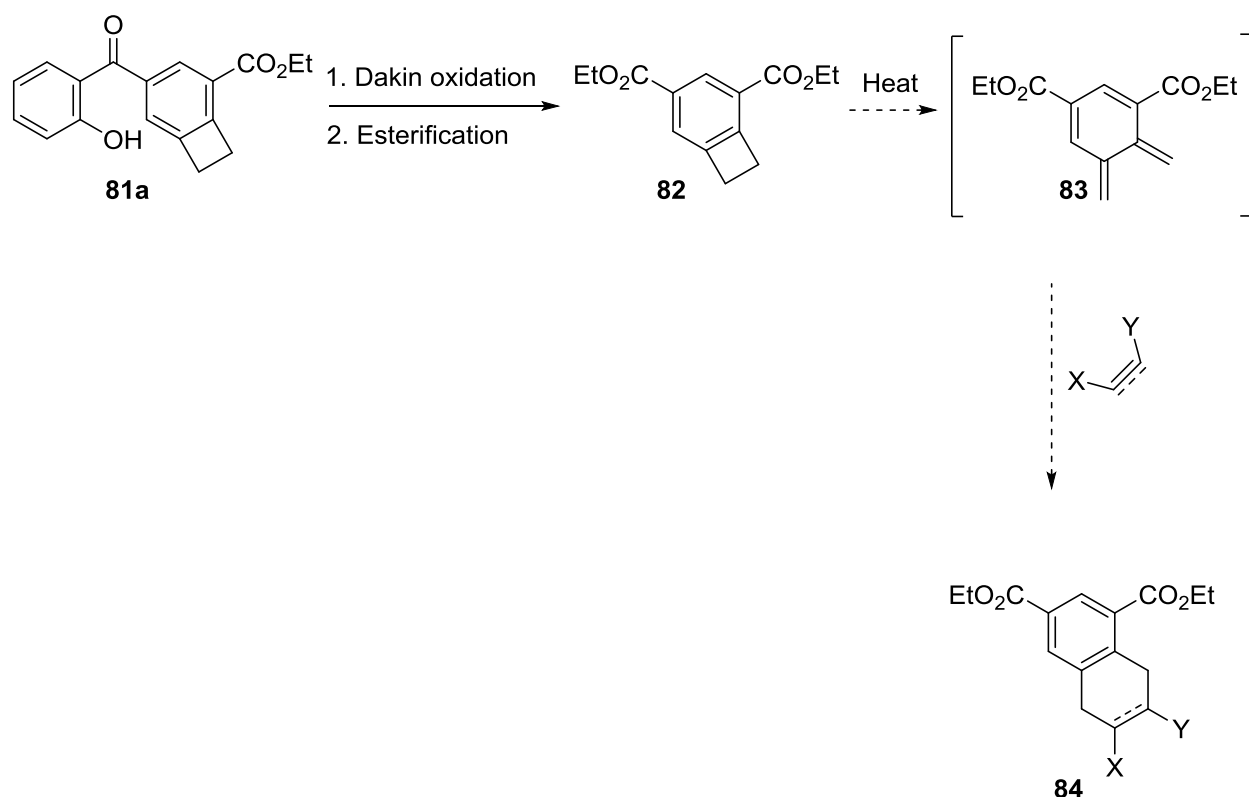
Prior to this work, both the *in situ* and preformed methods had been used to synthesize cycloalkane-fused compounds (2-hydroxybenzophenones). For enamines derived from C₅ and C₆ (Table 2.1)⁷ entries 2 and 3, both methods gave good yields of the 2-hydroxybenzophenones derivatives. For enamines derived for C₇ and C₈, only the preformed method afforded the derivatives produced (Table 2.1, Entries 4 and 5). In the case of the C₈-derived enamines, the yield was poor. The C₄-derived enamine is known to be very difficult to synthesize, so only the *in situ* method was employed and it gave the 2-hydroxybenzophenones in rather low yield (26%) (Table 2.1, Entry 1).

Table 2.1 Reaction of diene **63** with the *in situ* generated and preformed enamines



Entry	n	Time (h)	% Yield <i>In situ</i> Method	% Yield Preformed Method	Product
1	1	1.0	26	--	81a
2	2	0.25	85	78	81b
3	3	25	80	84	81c
4	4	24	n.r.	79	81d
5	5	24	n.r.	10	81e

Derivative **81a** was identified as an attractive target because it is a potential precursor to benzocyclobutene diester **82**. Thermal ring opening of **82** would give rise to *o*-xylylene **83**, which was envisaged as a reactive electron deficient diene for further IEDDA transformations (Scheme 2.9).⁷



Scheme 2.9 Potential application of hydroxybenzophenone **81a**.

Having established the fact that the initial preformed method of hydroxybenzophenone synthesis did not give rise to derivative **81a**, the initial *in situ* method of synthesis was also applied as the only suitable alternative for the synthesis of derivative **81a**. This method was successful for the synthesis of derivative **81a**, but the major drawback was the low yield (Table 2.1, Entry 1). Very low yields like 26% will not allow for further exploration of chemistry on derivative **81a**. The reaction mechanism for the formation of derivative **81a** was presented initially in Scheme 1.18.⁷

Related IEDDA reactions in the Bodwell group had been observed to respond very well to optimization, so work aimed at the improvement of the 26% yield for **81a**

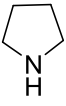
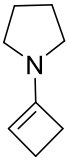
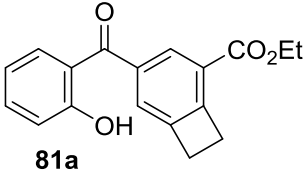
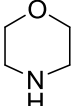
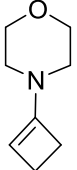
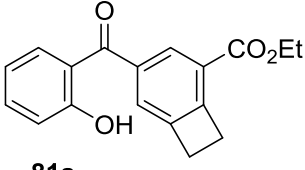
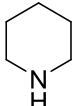
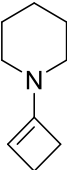
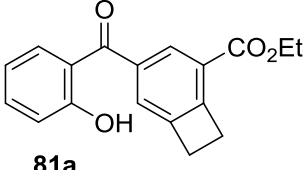
was initiated. The parameters that were varied include the secondary amine, the solvent, the number of equivalents of the secondary amine, the number of equivalents of the ketone and the temperature.

2.4.1 Secondary amine for reaction optimization

A small set of secondary amines (pyrrolidine, piperidine and morpholine) was employed in the reaction leading to **81a**. Using the original conditions for the synthesis of **81a**, yield went from 26% with pyrrolidine, to 50% with morpholine to 84% with piperidine (Table 2.2).

To try and understand the cause of the great variation in yield, the nature of the three enamines was considered. Stork reported in his earlier work on enamines that pyrrolidine-based enamines are more reactive towards electrophiles than piperidine-based enamines, which in turn are more reactive than morpholine-based enamines. The general order of reactivity by Stork as recorded in the literature is as follows: pyrrolidine > piperidine > morpholine.⁸ The higher reactivity of pyrrolidine-based enamines compared to their piperidine-based analogues has been explained by the higher p-character of a nitrogen lone pair in a five-membered ring compared to that of a six-membered ring, as evidenced by a lower first vertical ionization potential of pyrrolidino compounds than the corresponding piperidino compounds.⁹ Replacement of a CH₂ group in piperidine by a more electronegative oxygen atom further increases the ionization potential and consequently reduces nucleophilicity of a morpholine-based enamines.⁹

Table 2.2 Effect of secondary amine on yields

Entry	Secondary amine	<i>In situ</i> -generated enamine	Yield (%)	Product
1	 85	 86	26	 81a
2	 87	 88	50	 81a
3	 89	 90	84	 81a

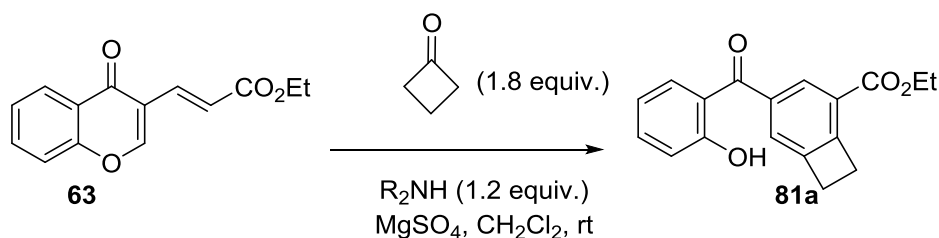
Curiously, the yields of the reactions leading to **81a** do not correlate with enamine reactivity. The most reactive enamine gave the lowest yield and the least reactive enamine gave the intermediate yield. The moderately reactive piperidine-based enamine gave the best yield (Table 2.2). The reason(s) for this are not clear. Upon consideration of the

assumed reaction pathway (Scheme 1.18), several reactions occur on the way to **81a** and the secondary amine is involved at various points during the course of the reaction. Thus the effect of changing the secondary amine may have different (and contrasting) effects at its various points of involvement in the reaction (enamine formation, IEEDA reaction, 1,2-elimination of the amine).⁷

2.4.2 Solvents for reaction optimization

The three reactions described above were performed in dichloromethane. To probe the effect of the solvent, the same set of three reactions was conducted using four additional solvents: toluene, tetrahydrofuran (THF), 1,4-dioxane and acetonitrile.

Table 2.3 The effect of different solvents on reaction optimization

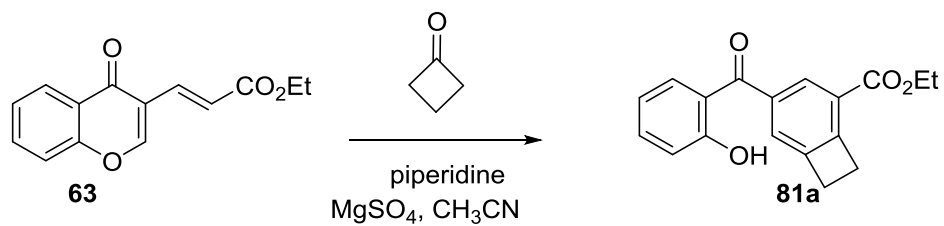


Entry	Solvent	Sec. amine	Time (h)	Yield (%)
1	dichloromethane	pyrrolidine	0.75	26
2	dichloromethane	piperidine	12	84
3	dichloromethane	morpholine	24	50
4	acetonitrile	pyrrolidine	5	31
5	acetonitrile	piperidine	6	85

6	acetonitrile	morpholine	13	56
7	tetrahydrofuran	pyrrolidine	6	39
8	tetrahydrofuran	piperidine	12	65
9	tetrahydrofuran	morpholine	30	60
10	toluene	pyrrolidine	5	26
11	toluene	piperidine	5	46
12	toluene	morpholine	72	35
13	1,4-dioxane	pyrrolidine	48	36
14	1,4-dioxane	piperidine	23	42
15	1,4-dioxane	morpholine	xx	xx

For each of the five solvents, the best yield was obtained with piperidine as the secondary amine and the lowest yield was obtained with pyrrolidine. It is worth noting that dichloromethane is known to react slowly with pyrrolidine, which may account for the lower yields using pyrrolidine.⁷ The observed yield for the reaction spanned a rather broad range, i.e. 42% in 1,4-dioxane, 85% in acetonitrile. A virtually equal yield (84%) was obtained using dichloromethane, but the reaction proceeded more rapidly in acetonitrile (6 h) than it did in dichloromethane (12 h) (consumption of **63**, tlc analysis).

Table 2.4 Piperidine-acetonitrile combination



Entry	2°. amine (equiv.)	Cyclobutanone (equiv.)	Time (h)	Yield (%)
1	1.2	2.5	4	66
2	1.2	1.2	4	81
3	2.5	1.8	12	69
4	0.25	1.8	18	84

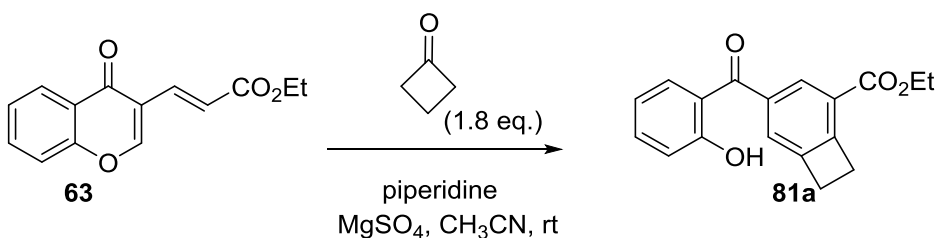
N/B: Yields were isolated yields

The piperidine/acetonitrile combination was chosen for further optimization work, not only because of the faster reaction, but also because of the higher boiling point of acetonitrile (82 °C). This left the door for the investigation of a broader temperature range than in the lower boiling dichloromethane (40 °C).

2.4.3 The number of equivalents of the secondary amine

A series of experiments was conducted to determine the effect of varying the number of equivalents of the secondary amine (piperidine) (Table 2.5). Very good yields (84-88%) were obtained between 0.25 and 1.2 equivalents, with the best yield coming from the reaction with 0.5 equivalents. Decreasing the number of equivalents below 0.25 resulted in a steady drop in the yield and a slowing of the reaction. Even at 0.05 equivalents (5 mol%), the reaction still proceeded meaningfully (39%), which means that it can be thought of as organocatalytic. In contrast to the trend toward increasing rate of consumption of **63** with increasing equivalents of piperidine, increasing the number of equivalents from 1.2 to 2.5 resulted in a drop in yield to 66% and an increase in the time required for the consumption of **63** (12 h). The reason for this seemingly anomalous behaviour is unclear.

Table 2.5 Effects of varying the number of equivalents of secondary amine on yield



Entry	Sec. amine	Equivalents	Reaction time (h)	Yield (%)
1	piperidine	2.5	12	66
2	piperidine	1.2	6	85
3	piperidine	0.5	12	88
4	piperidine	0.25	16	84

5	piperidine	0.10	18	66
6	piperidine	0.05	168	39
7	piperidine	0.01	168	2
9	piperidine	0	48	n.r.

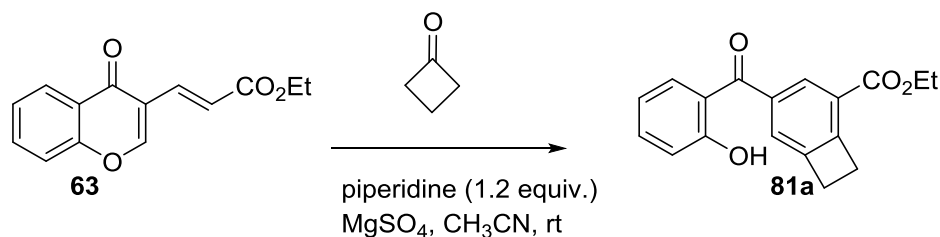
The significant progress of the reaction with as little as 5 mol% of the piperidine provides further evidence for a catalytic function of the secondary amine. As shown previously, the liberation of secondary amine from the initial IEDDA adduct (Scheme 1.18) provides a pathway through which the secondary amine can act as an organocatalyst.⁷

2.4.4 The number of equivalents of the ketone

Varying the number of equivalents of the ketone also had a significant effect on the reaction outcome. The reason for using 1.8 equivalents of the cyclobutanone up to this point was that this was the amount that had been used in the work original performed by Krista Hawco.¹⁷ It had been established earlier that the reaction involving 1.2 equivalents of piperidine and 1.8 equivalents of cyclobutanone in acetonitrile gave **81a** in 85% yield (Table 2.3, Entry 3; Table 2.6, Entry 2). Upon decreasing the number of equivalents of cyclobutanone to 1.2 (a little more than the 1.0 equivalents required by the stoichiometry of the reaction), the yield fell slightly to 81% (Table 2.6, Entry 3). The yield also fell when the number of equivalents of cyclobutanone was increased to 2.5. In this case the

yield was 66% (Table 2.6, Entry 1). Therefore, 1.8 equivalents is close to the optimal value.

Table 2.6 Effect of varying the number of equivalents of the ketone

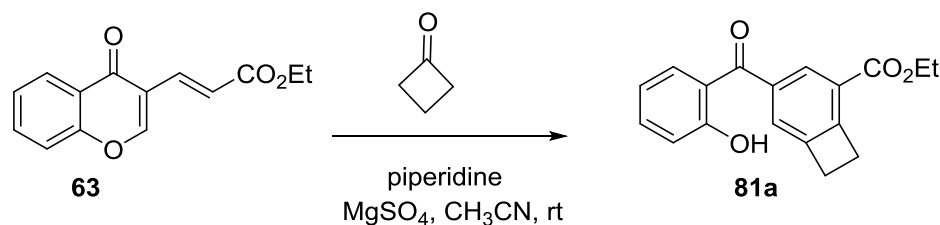


Entry	Secondary amine	Equivalents of ketone	Reaction time (h)	Yield (%)
1	piperidine	2.5	4	66
2	piperidine	1.8	6	85
3	piperidine	1.2	4	81

2.4.5 Temperature change on reaction optimization

Up to this point, the best yield of **81a** had been obtained using 1.8 equivalents of the ketone, 0.5 equivalents of the secondary amine and acetonitrile as the reaction solvent. Employing these conditions, a small set of reactions was carried out at different temperatures to establish the effect of temperature (Table 2.7)

Table 2.7 Effect of temperature change on reaction yield



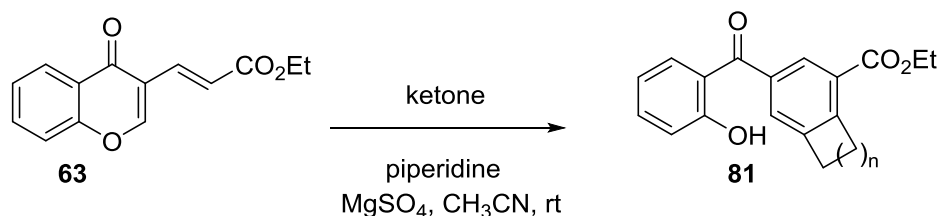
Entry	Ketone (equiv.)	Sec. amine (equiv.)	Temperature (0 °C)	Yield (%)	Time (h)
1	1.8	0.5	0	69	24
2	1.8	0.5	22	88	12
3	1.8	0.5	40	84	4
4	1.8	0.5	60	39	1

As would be expected, the apparent rate of reaction increased with increasing temperature. Thus the reaction at 0 °C took 24 h and afforded **81a** in 69% yield (Table 2.7, Entry 1). At 22 °C, the yield improved to 88% but took only 12 h (Table 2.7, Entry 2). Increasing the temperature to 40 °C resulted in a 4 h reaction that gave **81a** in 84% yield (Table 2.7, Entry 3). Although a further increase in temperature to 60 °C reduced the reaction time to just 1 h, the yield dropped sharply to 39% (Table 2.7, Entry 4). Again, the complex nature of the reaction makes it difficult to draw concrete conclusions about what underlies the variation in yield. Whatever the case, room temperature and slightly above appears to be the optimal temperature range.

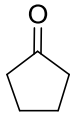
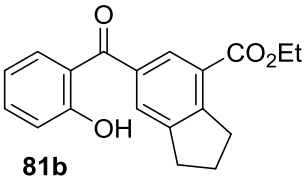
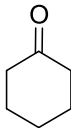
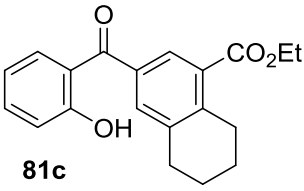
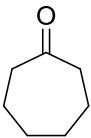
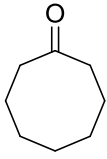

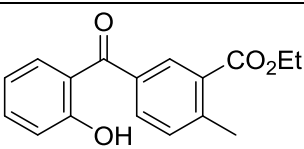
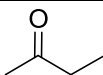
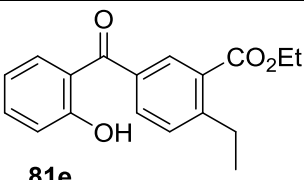
2.5 IEDDA reaction with ketones within the scope of work

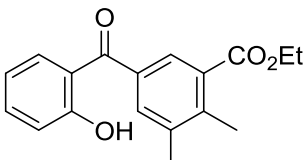
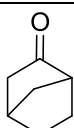
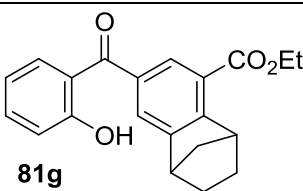
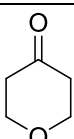
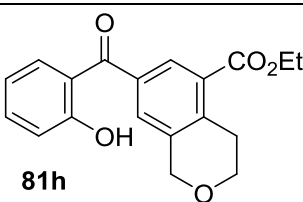
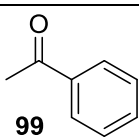
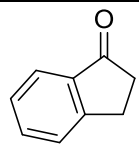
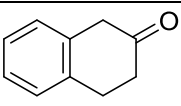
Having established that the best yield was obtained using piperidine as the secondary amine (0.5 equivalents), acetonitrile as the solvent, 1.8 equivalents of the ketone and room temperature or 40 °C as the best temperature, these conditions were adopted as the optimized conditions. These conditions were then applied to the reaction of diene **63** with a variety of ketones other than cyclobutanone. For each ketone separate reactions were performed at room temperature and at 40 °C. The results are summarized in Table 2.8.

Table 2.8 Optimized results using conditions [A] and [B]



Entry	Ketone	Optimized Condition [A] (rt.)		Optimized Condition [B] (40 °C)		Product formed
		Yield	Time	Yield	Time	
1		88%	18 h	80%	16 h	
	79	90% ^a	18 h ^a	--	--	

2	 <p>91</p>	88%	20 h	86%	18 h	 <p>81b</p>
3	 <p>92</p>	45%	24 h	86%	23 h	 <p>81c</p>
4	 <p>93</p>	n.r.	48 h	n.r.	48 h	product not formed
5	 <p>94</p>	n.r.	48 h	n.r.	48 h	product not formed
6	 <p>95</p>	81%	18 h	62%	16 h	 <p>81d</p>
7	 <p>96</p>	65%	24 h	63%	24 h	 <p>81e</p>

					 81f	
8	 97	65%	31 h	63%	29 h	 81g
9	 98	81%	24 h	78%	22 h	 81h
10	 99	n.r.		n.r.		Product not formed
11	 100	n.r.		n.r.		Product not formed
12	 101	n.r.		n.r.		Product not formed

n.r.: Indicates no reaction took place

N/B: Yields were isolated yields

90%^a: Indicates large scale reaction with ketone **79**

The reactions were monitored by tlc and reaction times given correspond roughly to the time taken for the last trace of the starting material (**63**) to disappear. Going through the entries in Table 2.8, the reaction with cyclobutanone (**79**) (Entry 1, Table 2.8) represents the best result from the optimization work. All of this work was performed using 200 mg of **63**. Upon increasing the scale of this reaction to 2 g of **63**, the yield increased slightly to 90%. At 40 °C, a small decrease in the yield (80%) occurred. Cyclopentanone (**91**) (Entry 2, Table 2.8) reacted with **63** to furnish **81b** in excellent yields both at room temperature (88%, 20 h) and at 40 °C (86%, 18 h). Cyclohexanone (**92**) reacted with **63** (Entry 3, Table 2.8) to afford derivative **81c** in only moderate yield at room temperature (45%, 24 h) but the yield of **81c** improved greatly when the reaction was performed at 40 °C (86%, 23 h).

Clearly, the outcome of the reaction is strongly influenced by the size of the cycloalkanone. According to tlc analysis, the reactions involving cyclobutanone and cyclopentanone proceeded considerably more quickly than the corresponding reaction with cyclohexanone during the first several hours, but the time required for the complete consumption of **63** was not markedly different for the three homologous ketones. The use of cycloheptanone (**93**) (Table 2.8, Entry 4) and cyclooctanone (**94**) (Table 2.8, Entry 5) did not lead to the formation of the desired product either at room temperature or at 40 °C

To gain some understanding of the differences in behaviour of the various cycloalkanones, it would be useful to consider the rate-determining step. It may be assumed that the rate-determining step is the initial IEDDA reaction because only the starting material and products are observed during the course of the reactions (tlc

analysis). Both reaction components have electronically biased π systems, so a strongly asynchronous transition state can be expected, i.e. with much more advanced bond formation between the more highly charged carbon atoms of the diene and dienophile (see Figure 1.2, Figure 2.1). The IEDDA reaction can also proceed through an *endo* or an *exo* (with respect to the NR_2 group) transition state, but in either case the steric interactions between the oxygen atom of the chromone system and the allylic CH_2 group of the enamine appear to be an important factor according to the examination of simple molecular models. In the cyclobutanone-derived enamine, the *ca.* 90° bond angles in the 4-membered ring mean that the allylic CH_2 group is further from the chromone oxygen atom of the diene than the corresponding CH_2 group in the cyclopentanone derived enamine, in which the bond angle is *ca.* 112° .¹⁰ In moving to the cyclohexanone derived enamine, the bond angle is about 120° , which means that the allyl CH_2 group is even closer to the chromone oxygen atom. A further point is that the cyclobutanone and cyclopentanone derived enamines are planar, or close to planar respectively, whereas the higher homologs are not. This means that other CH_2 groups can conceivably come into play during the approach of the two reaction components. A detailed computational study would surely provide more concrete conclusions than the speculative thoughts provided here.

Unlike with the cycloalkanones, carrying out the reaction using acetone (**95**) and 2-butanone (**96**) employing the optimized conditions, the reactions failed to progress even minimally (tlc analysis). This is perhaps surprising because the two ketones are not significantly different from the cycloalkanones electronically and the enamines that they

should form would be expected to be sterically undemanding. When acetone (**95**) and 2-butanone (**96**) were used as both a reactant ketone and as the solvent, the reaction proceeded smoothly to afford their respective products. Acetone (**95**) (Table 2.8, Entry 6) afforded **81d** in good yield (81%, 18 h) at room temperature and in moderate yield at 40 °C (62%, 16 h). 2-butanone (**96**) (Table 2.8, Entry 7) gave rise to a mixture of derivatives **81e** and **81f** in a ratio of (1:1) with a combined yields of (65%, 24 h) at room temperature, and (63%, 23 h) at 40 °C. The product mixture arises because 2-butanone is capable of forming two different enamines. The *ca.* 1:1 product distribution is surprising because enamine formation/reaction normally favors the less substituted enamine. For example, the organocatalytic reaction of 2-butanone with aldehyde **111** in the presence of (*L*)-proline gave β -hydroxyketone **112** in 65% yield (Scheme 2.10).¹¹ Reaction occurred only through the less substituted enamine of **96**. It is not clear why such a significant proportion of the reaction of **96** with **63** proceeded through the more substituted enamine.

A selection of other ketones was then subjected to reaction with diene **63**. 2-norbornanone (**97**) (Table 2.8, Entry 8) afforded **81g** in 65% yield at room temperature (32 h) and 63% yield at 40 °C (30 h). Tetrahydro-4*H*-pyran-4-one (**98**) (Table 2.8, Entry 9) gave **81h** in good yield both at room temperature (81%, 24 h) and at 40 °C (78%, 20 h). Acetophenone (**99**), 1-indanone (**100**) and 2-tetralone (**101**) all failed to react with diene **63** after 48 h (tlc analysis) at room temperature and at 40 °C. The ketones and the diene were recovered. For the aryl ketones **99**, and **100**, enamine formation by azeotropic removal of water is known to be very difficult, so the lack of reactivity here is likely a reflection of the nature of the ketones.¹² Enamines of acetophenone is unstable and

rapidly polymerizes in the presence of a trace of acid.¹² The poor reactivity of 2-tetralone derived enamines, which are actually commercially available, may be attributed to steric interactions between the oxygen atom of the chromone system of the diene and the aromatic proton *ortho* to the enamine formed by 2-tetralone (Figure 2.2).

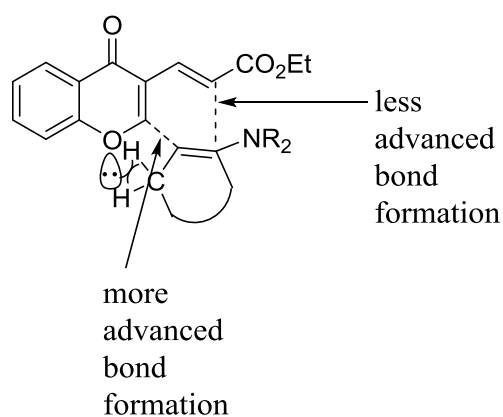
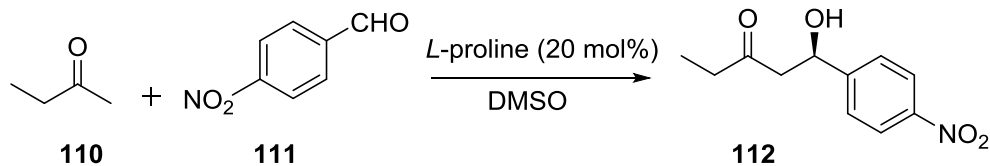


Figure 2.1 Bond formation between diene **63** and enamines



Scheme 2.10 Organocatalytic reaction of 2-butanone **110** with 4-nitrobenzaldehyde **111**

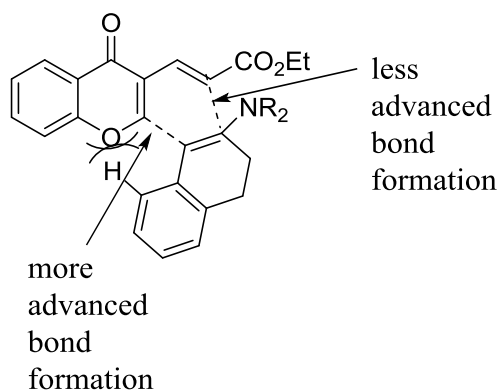
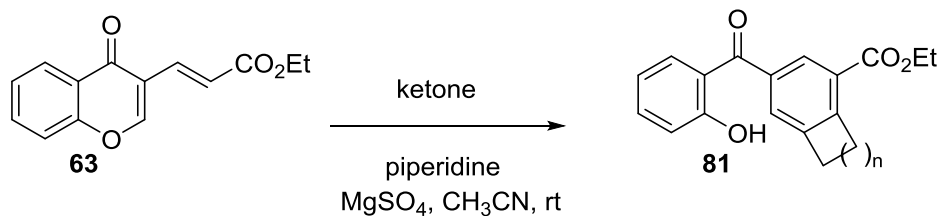


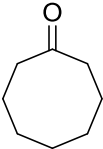
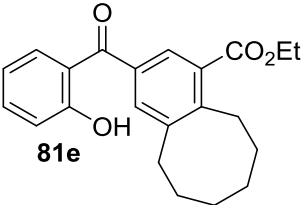

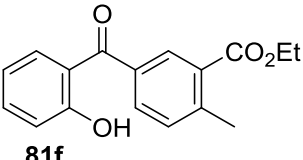
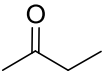
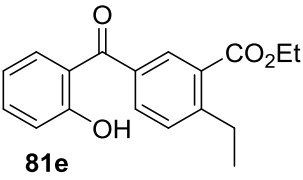
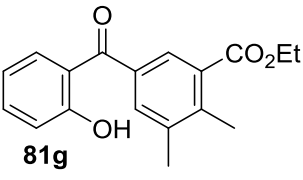
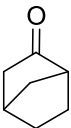
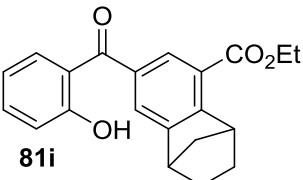
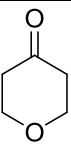
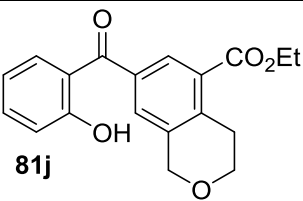
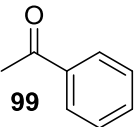
Figure 2.2 Bond formation between diene **63** and enamine of 2-tetralone

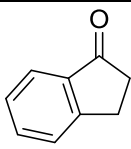
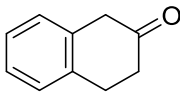
With a set of results using the optimized conditions (Table 2.9, Conditions A), comparisons could be made with the result using the original *in situ* conditions (Table 2.9, Conditions B)¹⁷ and those obtained using preformed enamines (Table 2.9, Conditions C).¹⁷ Upon examination of Table 2.9, it is clear that the optimized *in situ* conditions give superior yields than the original *in situ* conditions, except for the case of acetone **95** (Table 2.9, Entry 6). In this instance, the yields were both good (Conditions A, 81%; and Conditions B, 87%) and acetone was used as both reactant ketone and solvent in optimized condition A. The optimized *in situ* condition were also consistently superior to the preformed conditions (Conditions C),¹⁷ except when no reaction occurred using Conditions A, e.g. with cycloheptanone (**93**) as the ketone (Condition A; n.r.; Conditions C, 78%).

Table 2.9 Comparison of yields using the optimized *in situ* Conditions [A], the original *in situ* Conditions [B]¹⁷ and the original preformed Conditions [C].¹⁷



Entry	Ketone	[A]	[B]	[C]	Product formed
1	 79	90%	26%	n.r.	 81a
2	 91	88%	85%	78%	 81b
3	 92	86%	80%	84%	 81c
4	 93	n.r.	n.r.	79%	 81d

5	 94	n.r.	n.r.	10%	 81e
6	 95	81%	87%	n.r.	 81f
7	 96	65%	--	--	 81e  81g
8	 97	65%	54%	--	 81i
9	 98	81%	78%	--	 81j
10	 99	n.r.	--	--	product not formed

11	 100	n.r.	--	--.	product not formed
12	 101	n.r.	--	--	product not formed

Conditions A Optimized *in situ* conditions

Conditions B Previous *in situ* conditions¹⁷

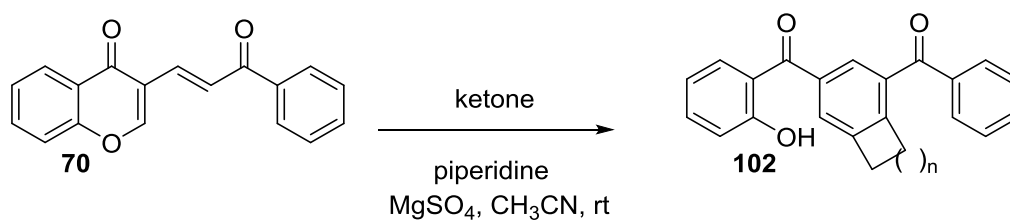
Conditions C Previous preformed conditions¹⁷

n.r. Indicates no reaction

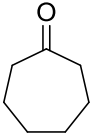
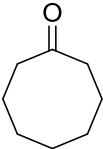

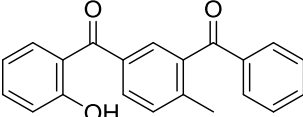
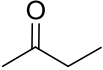
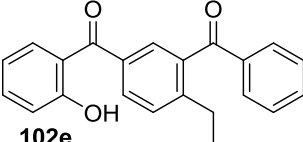
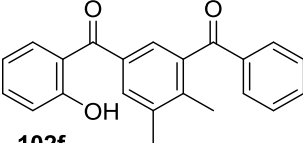
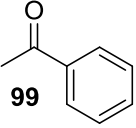
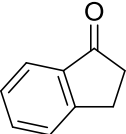
Similar IEDDA reactions were also carried out using chromone-fused diene **70** employing the optimized *in situ* conditions. The outcome of the reactions with chromone fused diene **70** using the optimized conditions were presented in Table 2.10, (Conditions A) along with previous results using the original *in situ* conditions (Table 2.10, Condition B)¹⁷ and other results obtained previously using the preformed enamines (Table 2.10, Conditions C).¹⁷ As with diene **63**, the outcome of the best results were obtained using the optimized *in situ* results (Conditions A). The advantage of using Conditions A was again most pronounced when cyclobutanone **79** was used as the ketone (Table 2.10, Entry 1). Here the yield improves from 15% using Conditions B¹⁷ to 96% using Condition A. A less dramatic, but still very substantial increase in yield was achieved in the case of

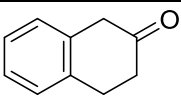
cyclopentanone (Conditions B: 30%; Conditions A: 83%) (Table 2.10, Entry 2). Not surprising, no reaction occurred using acetophenone **99**, 1-indanone **100**, 2-tetralone **101** e.t.c. For 2-butanone **96**, the ratio of the two products was again 1.1:1

Table 2.10 Comparison of yields using the optimized *in situ* Conditions [A], the original *in situ* Conditions [B]¹⁷ and the original preformed Conditions [C].¹⁷



Entry	Ketone	[A]	[B]	[C]	Product formed
1	 79	96%	15%	--	 102a
2	 91	83%	30%	83%	 102b
3	 92	86%	80%	71%	 102c

4	 93	n.r.	n.r.	--	product not formed
5	 94	n.r.	n.r.	--	product not formed
6	 95	87%	--	--	 102d
7	 96	63%	--	--	 102e ratio 1.1:1  102f
8	 99	n.r.	--	--	product not formed
9	 100	n.r.	n.r.	--.	product not formed

10	 101	n.r.	n.r.	n.r.	product not formed
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Conditions A Optimized *in situ* conditions.

Conditions B Previous *in situ* conditions.¹⁷

Conditions C Previous preformed conditions.¹⁷

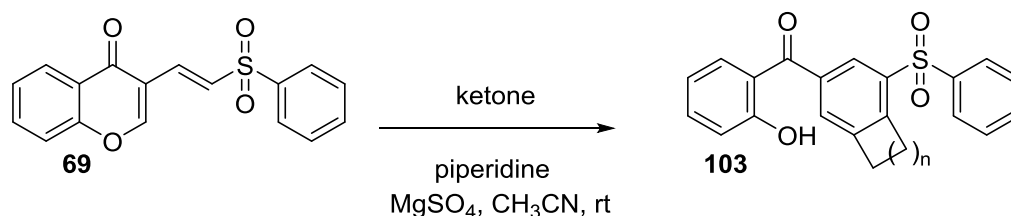
N/B: Yields were isolated yields

n.r. indicates no reaction

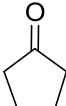
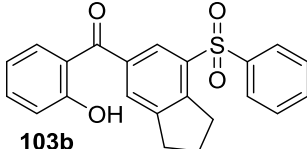
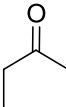
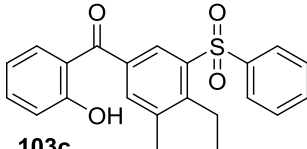
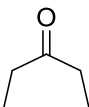
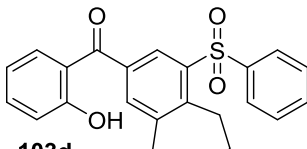
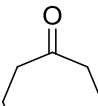

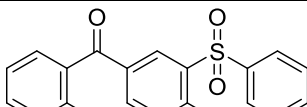

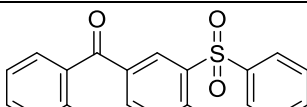
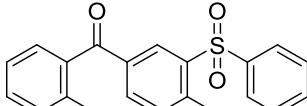
No prior work had been done with diene **69** using Conditions B,¹⁷ so the results of the reaction of diene **69** employing the optimized *in situ* conditions (Conditions A) can only be compared to those using preformed enamines (Conditions C)¹⁷ (Table 2.11). As for diene **63** and **70**, the best results were obtained using the optimized *in situ* conditions (Conditions A) in most of the cases. The only exception is in the case where Conditions A resulted to no reaction. Compound **103a** (Table 2.11, Entry 1) was not synthesized using a preformed enamine (Conditions C),¹⁷ but the advantage of using Conditions A presented itself again. Compound **103a** was obtained in 82% yield (Table 2.11, Entry 1). An increase in yield was also achieved working with cyclopentanone **91** (Table 2.11, Entry 2) using Conditions A. Optimized *in situ* Conditions A gave an excellent yield of 95% yield against 83% yield using Conditions C.¹⁷ The same outcome was obtained working with cyclohexanone **92** (Table 2.11, Entry 3). Conditions A gave yield of 80% yield, but Conditions C¹⁷ gave just a 67% yield of the same compound **103c**. As before Conditions C¹⁷ gave rise to compound **103d** in 76% yield working with the pyrrolidine-

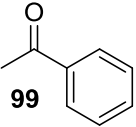
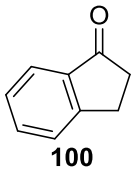
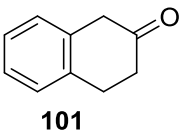
derived enamine cycloheptanone **93** (Table 2.11, Entry 4), but the use of conditions A resulted in no reaction. This is the only case where Conditions A do not give the best result. It is not surprising that no reaction occurred using acetophenone **99**, 1-indanone **100** and 2-tetralone **101** (Table 2.11, entries 8,9 and 10). Acetone (**95**) and 2-butanone (**96**) were used both as a reagent and solvent under Conditions A. This gave rise to **103e** in 83% yield (Table 2.11, Entry 6) and a 1.1:1 mixture of **103f** and **103g** (Table 2.11, Entry 7). The ratio of **103f:103g** is exactly the same as for **102e:102f** and **81e:81g**, which suggest that the nature of the electron withdrawing group on the chromone fused diene skeleton has essentially no effect on the product distribution.

Table 2.11 Comparison of yields using the optimized *in situ* Conditions [A] and the original preformed Conditions [C]¹⁷



Entry	Ketone	[A]	[B]	[C]	Product formed
1	 79	82%		n.r.	 103a

2	 91	95%		83%	 103b
3	 92	80%		67%	 103c
4	 93	n.r.		76%	 103d
5	 94	n.r.		--	product not formed
6	 95	83%		n.r.	 103e
7	 96	61%		--	 103f ratio 1.1:1  103g

8	 99	n.r.		--	product not formed
9	 100	n.r.		--	product not formed
10	 101	n.r.		--	product not formed

Conditions A Optimized *in situ* conditions.

Conditions B Previous *in situ* conditions.¹⁷

Conditions C Previous preformed conditions.¹⁷

N/B: Yields were isolated yields

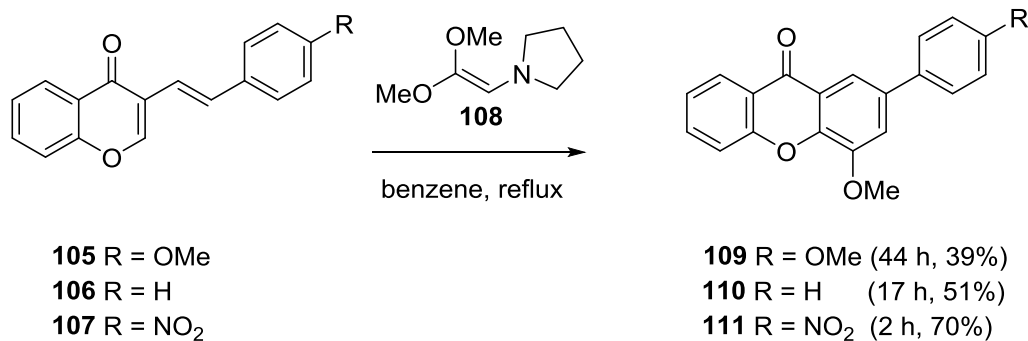
n.r. Indicates no reaction

In looking at the results for diene **63,70** and **69**, it can be seen that the optimized *in situ* conditions (Conditions A) gave better results than both the original *in situ* conditions (Conditions B) and the preformed enamine conditions (Conditions C) in most cases. Not surprisingly, the most dramatic improvement were obtained using cyclobutanone, which is the ketone for which the optimization work was done. Both sets of *in situ* conditions fail for cycloalkanones larger than cyclohexanone, in which case the use of a preformed enamine is necessary. Ketones **99-101** consistently failed to give the

desired product using *in situ* conditions (Conditions A, and Conditions B), which further limits the scope of the methodology.

2.6 Pyridinyl-fused diene **104**

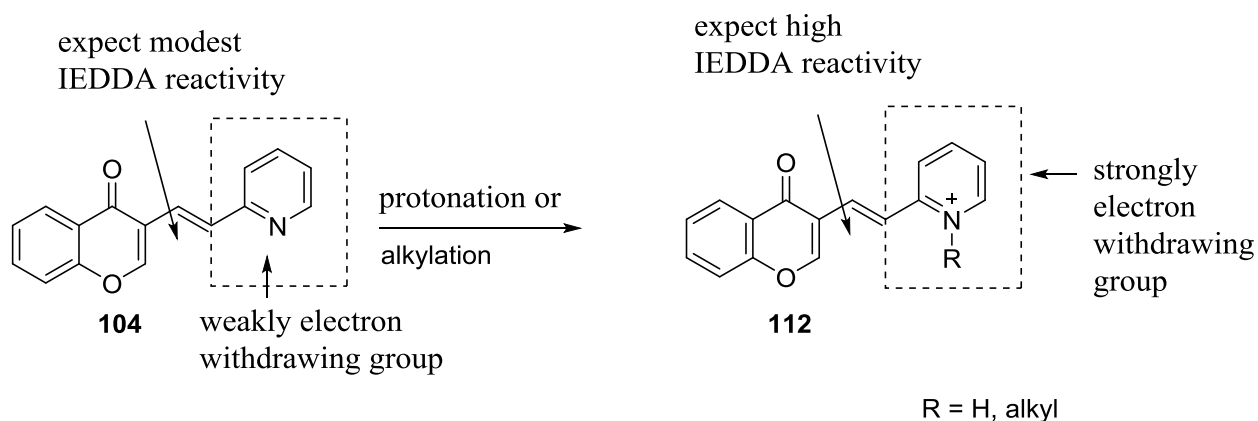
In the final part of this Chapter, work aimed at the synthesis of chromone-fused diene **104** is presented. A previous member of the Bodwell group, Anh-Thu Dang, synthesized chromone-fused dienes **105-107** using the Doebner modification of the Knoevenagel condensation. Dienes **105-107** were reacted with electron rich dienophile **108** to afford 4-methoxyxanthenes **109-111** by way of an IEDDA/double elimination reaction.¹³ In going from the most electron rich diene **105** to most electron deficient diene **107**, both the rate of the reaction and the yield of the product increased considerably (Scheme 2.11).¹³



Scheme 2.11 IEDDA reactions of dienes **105-107** with dienophile **108** to afford methoxyxanthenes **109-111**.

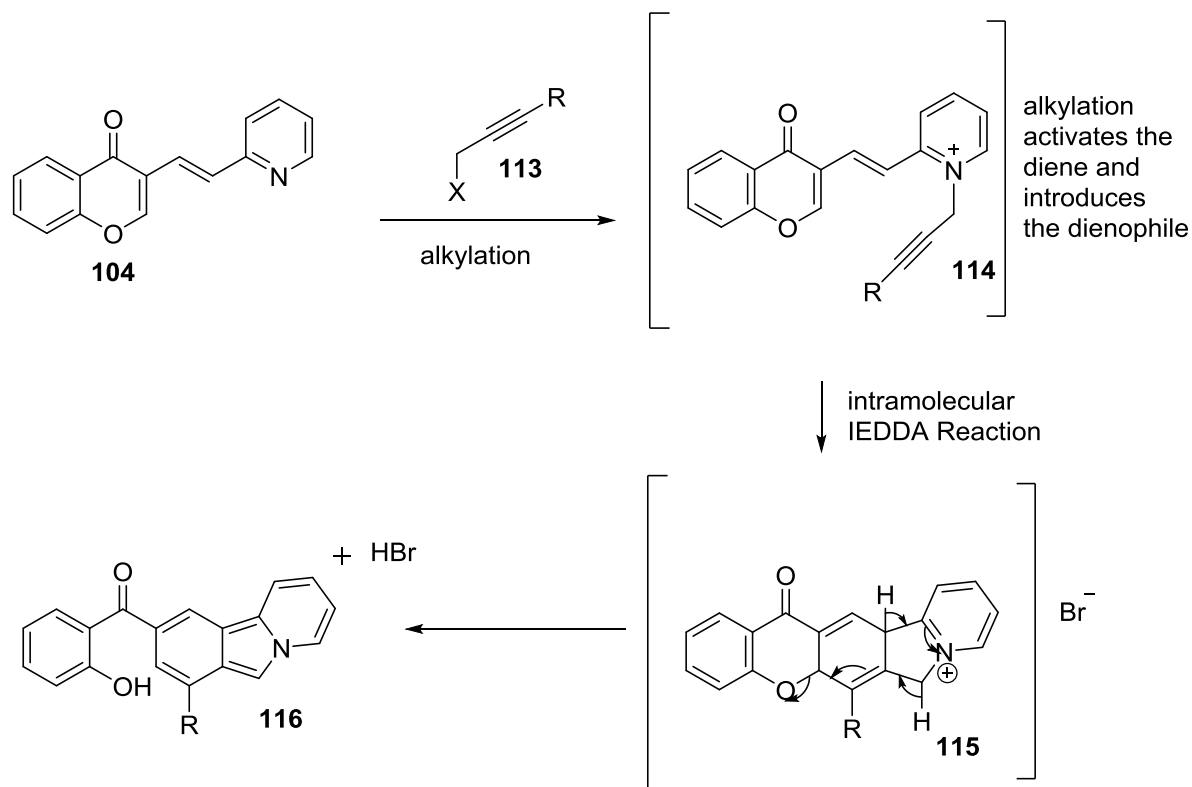
Beyond the introduction of electron withdrawing groups, another way to make an aromatic system more electron deficient is to replace a skeletal carbon atom with a nitrogen atom. Thus, pyridine-containing diene **104** would be expected to be a slightly

better diene than **106** in the IEDDA reaction. However, unlike **106**, diene **104** can be protonated or alkylated to give a much more electron-deficient system **112**. As such, diene **112** would be expected to be a very reactive diene in the IEDDA reaction. (Scheme 2.12)



Scheme 2.12 Alkylation reaction of diene **104**.

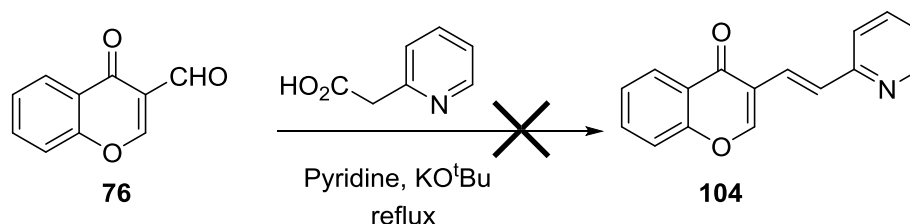
The use of a 2-pyridyl group in **104** places the N atom in a position where the alkylation reaction can be used to simultaneously activate the diene and introduce the dienophile. For example, alkylation of **104** with a propargylic halide **113** should give rise to positively charged diene **114** (Scheme 2.13). Intramolecular IEDDA reaction would be expected to afford adduct **115**, which could conceivably collapse as shown to afford pyrido[2,1-a]isoindole **116**. The pyrido-isoindoles are known to be selective serotonin reuptake inhibitors (SSRIS), which are known for their use in a variety of neurological disorders and also for the treatment of obsessive compulsive disorders.¹⁴



Scheme 2.13 Proposed synthesis of pyrido[2,1-*a*]isoindole derivative **116**.

The first attempt to synthesize **104** involved the use of the Doebner modification of the Knoevenagel condensation reaction. Accordingly, 3-formylchromone **76** was reacted with commercially available 2-pyridineacetic acid in the presence of ^tBuOK in

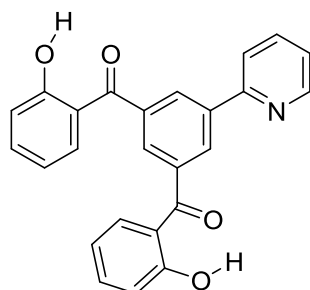
pyridine for 24 h (Scheme 2.14). No evidence for the formation of **104** was obtained.



Scheme 2.14 Attempted synthesis of diene **104** using the Doebner reaction.

Surprisingly, very little consumption of the starting material was observed (tlc analysis) and 95% of the 3-formylchromone was recovered by column chromatography. A small amount of a new compound was also isolated, but its ¹H NMR spectrum and mass spectrum were clearly inconsistent with the desired compound **104**, or any of the expected intermediates leading to it. The mass spectrum (APCI(+)) $m/z = 396$, APCI(-) $m/z = 394$) indicated that the new compound had a molar mass of 395. In the ¹H NMR spectrum, a singlet at δ 11.96 was reminiscent of OH signals for the 2-hydroxybenzophenones **81**, **102** and **103** described earlier ($\delta = 11.71$ - 12.17). A set of signals of the same integration as the signal at δ 11.96 (7.62 (d, $J = 1.6$ Hz, 1H), 7.65 (d, $J = 1.6$ Hz, 1H), 7.59-7.50 (m, 1H)), were consistent with protons of a 2-hydroxybenzophenone moiety. A coupled doublet and triplet ($J = 1.6$ Hz, 1H) with an integral ratio of 2:1 suggested that 1,3,5-trisubstituted benzene was present, in which two of the substituents were the same. The 2:1 integral ratio of the hydroxybenzophenone OH signal at δ 11.96 to the triplet at δ 7.98 suggested that two of the substituents of the 1,3,5 trisubstituted benzene were 2-hydroxybenzoyl groups. That the third substituent was a 2-pyridyl group was supported by the presence of a set of three signals at δ 8.73 (m, 1H),

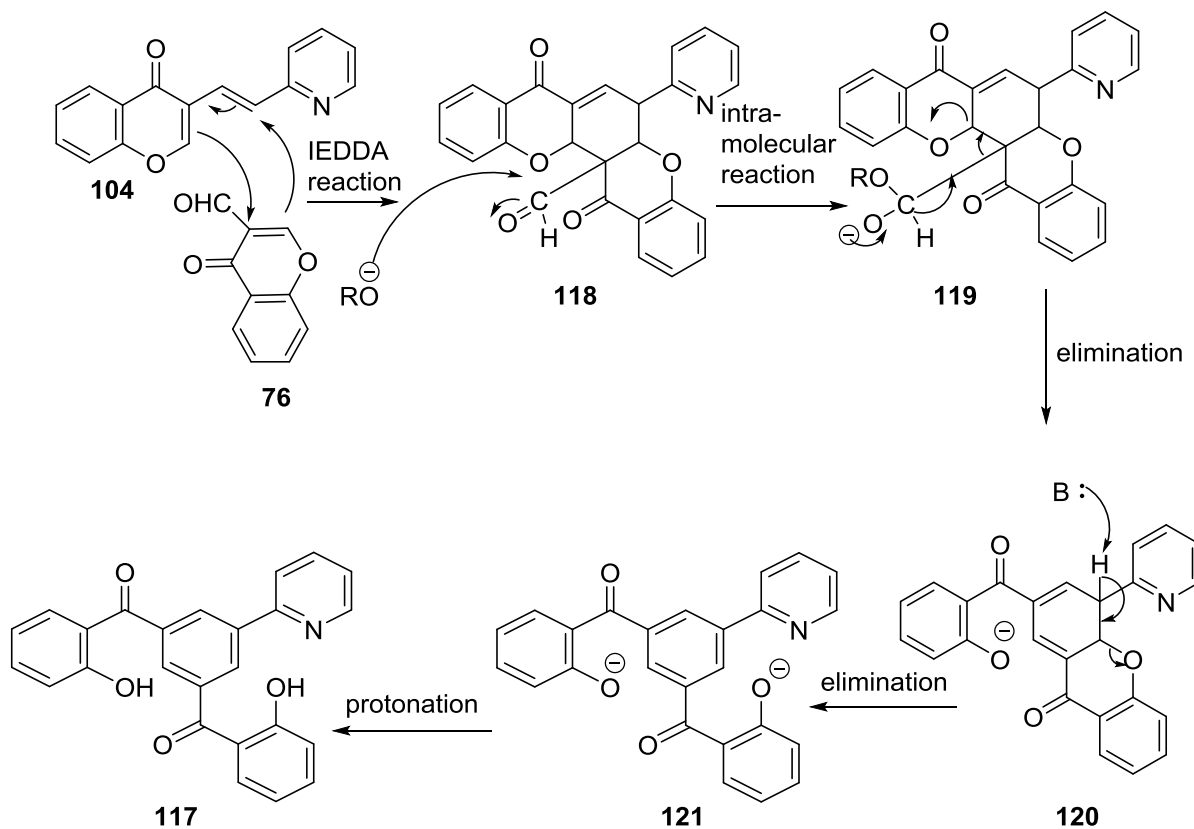
7.84 (m 2H), 7.37 (m, 1H) Thus the structure of the new compound was assigned as 1,3-bis (2-hydroxybenzoyl)-5-(2-pyridyl) benzene **117**, which has a molar mass of 395.



117

Figure 2.3 Structure of compound **117**.

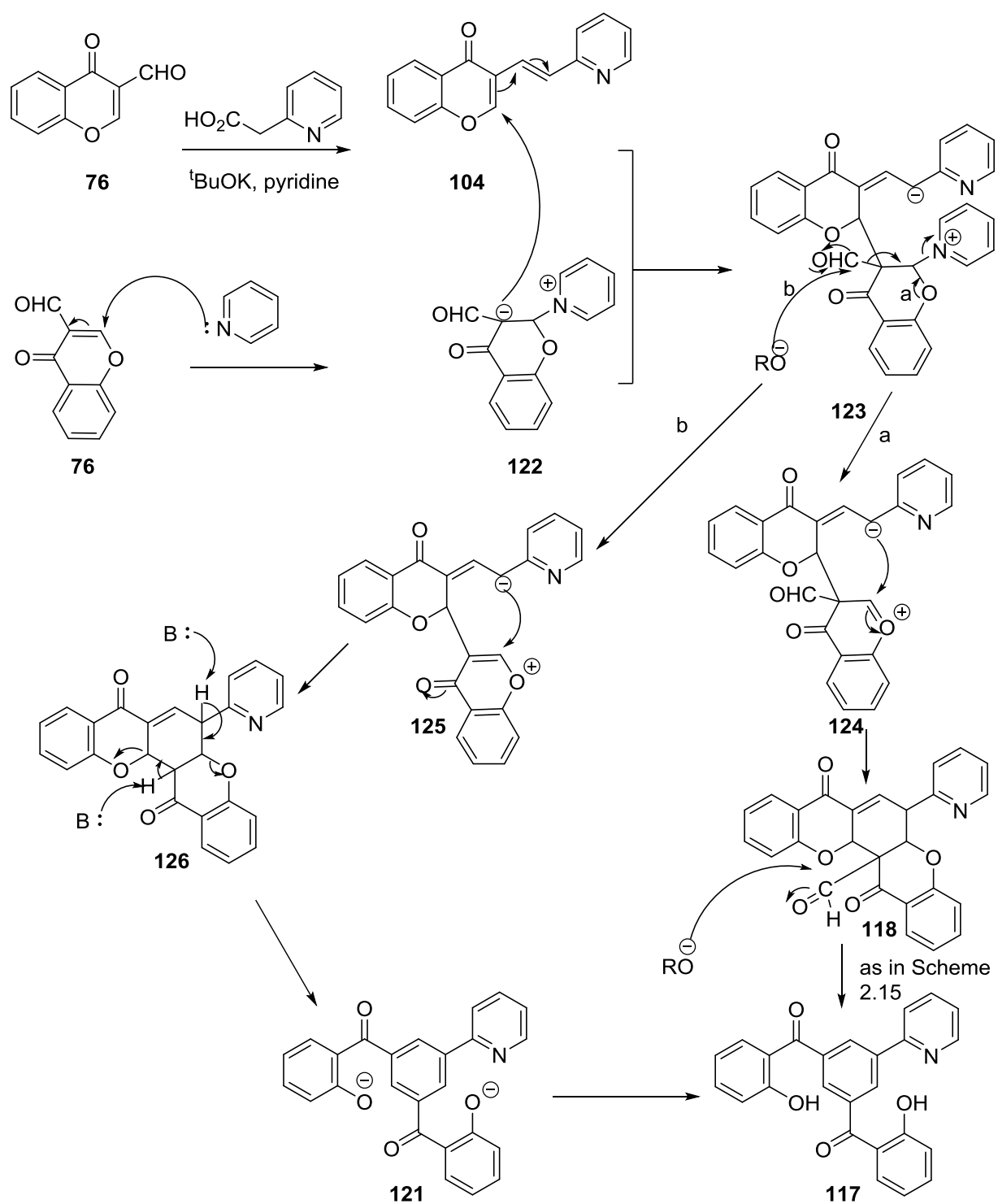
To explain how compound **117** forms, two equivalents of 3-formylchromone are clearly needed in the reaction pathway. Assuming that the desired diene **104** formed, a formal Diels-Alder reaction with 3-formylchromone would give adduct **118**, which could lead to **117** as shown in Scheme 2.15. Attack of the formyl group by a nucleophile such as t-butoxide could afford tetrahedral intermediate **119**, which could collapse as shown to afford diene **120**. A simple 1,2-elimination would then generate a new aromatic ring and protonation would afford compound **117**.



Scheme 2.15 Possible mechanism for the formation of compound **117**.

The Diels-Alder reaction between diene **104** and 3-formylchromone **76** doesn't look reasonable because both components of the reaction are electron deficient. A Bayliss-Hillman type of reaction¹⁵ may be more reasonable in this case (Scheme 2.16). Conjugate addition of pyridine to 3-formylchromone **76** would afford zwitter ion **122**, which could add nucleophilically to diene **104** at the most electron deficient site to give adduct **123**. At this point, several routes to **117** are conceivable, which mainly differ in the order of events. Two possibilities are shown in Scheme 2.16. According to path a,

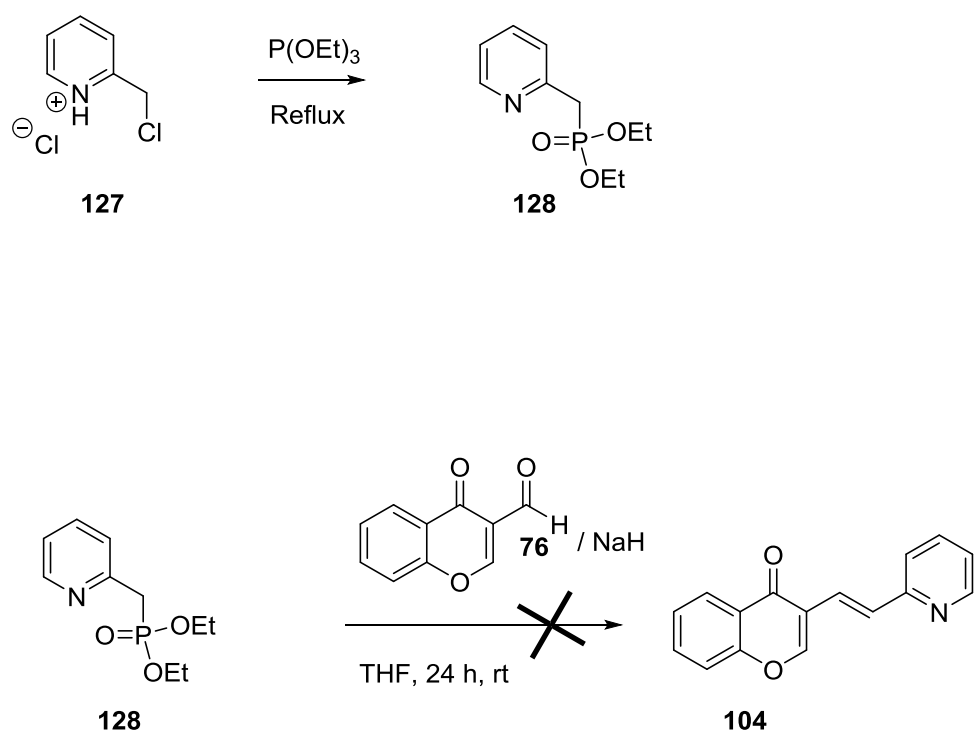
ejection of pyridine would afford oxcarbenium cation **124**, which could cyclize via an intramolecular 6-exo-trig cyclization to give **118**. Deformylation and elimination could then take place as shown in Scheme 2.16 to afford **117**. Alternatively, according to path b, initial deformylation of **123** would generate chromone **125**, which could cyclize to give **126**. Two elimination reactions would then afford **121** and then **117** upon protonation.



Scheme 2.16 Possible mechanism for the formation of **117** using Bayliss-Hillman reaction

For whatever reason, the formation of diene **104** appears to be slow, so a molecule of **104** that forms is exposed to an excess of 3-formylchromone **76** for extended period of time. Thus, the opportunity exists for **104** to proceed to **117**. The reason why the reaction leading to **104** is slow is unclear.

An alternative route to diene **104** was then investigated. This was based on the use of the HWE reaction (Scheme 2.17), which had been used successfully in the synthesis of other chromone-fused electron deficient dienes, e.g. **63**, **69** and **70**.¹⁷ To achieve the synthesis of **104**, phosphonate **128** (2-[(diethylphosphono)methyl]pyridine P-oxide) was required by the Arbuzov reaction of commercially available 2-picolylchloride hydrochloride (2-chloromethylpyridine hydrochloride) with triethyl phosphite. Phosphonate **128** was synthesized but could not be isolated in pure form. Specially, it could not be obtained without contamination by triethyl phosphite even using column chromatography. Triethyl phosphite did not show a separate spot in the tlc plate with **128** making its separation more difficult. HWE reaction of impure **128** with 3-formylchromone (**76**) unfortunately failed. The starting materials were recovered. The reason for the failure of this reaction is unclear as triethyl phosphite would not be expected to interfere with HWE reaction.



Scheme 2.17 Attempted synthesis of diene **104** using the HWE reaction.

2.7 Conclusions and Future Work

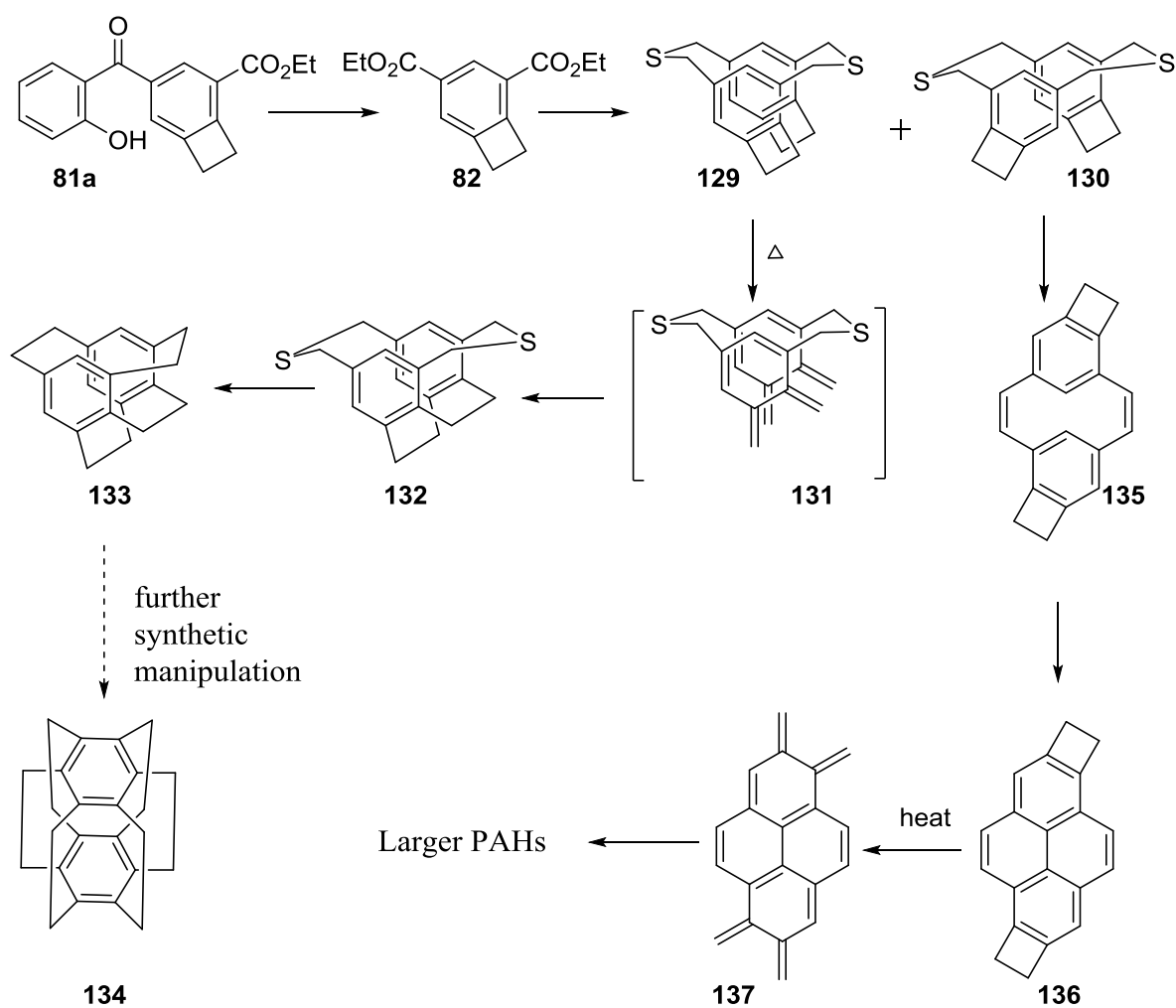
The major aim of this research work was the investigation of the scope and limitation of the IEDDA driven domino reactions of chromone-fused dienes **63**, **69** and **70** leading to 2-hydroxybenzophenones. In pursuing this objective, a variety of functionalized 2-hydroxybenzophenones was synthesized. The yield of compound **81a** was also optimized to be high yielding on a 2 g scale and these conditions were used for all subsequent work. Comparisons between the yields obtained using the new optimized *in situ* conditions, the initial *in situ* conditions and preformed enamines¹⁷ led to the conclusion that the new optimized conditions gave better yields in almost every case.

The scope of the reaction does not appear to be very broad with regards to the ketone that is used as an enamine precursor. Cyclic ketones with ring sizes of 4-6 work well, while no reaction is seen when the ketone is part of a larger ring. The fusion of benzene ring to a 5 or 6-membered cyclic ketone also shuts down the reaction. Steric effects are presumably responsible for the lack of reactivity. The acyclic ketones investigated were found to react slowly under the new optimized *in situ* conditions, but gave good yields when used as both solvent and reactant.

Attempts to synthesize pyridine-containing diene **104** were unsuccessful using the Doebner modification of Knoevenagel condensation and the HWE reaction. In the former case, a small amount of a very unusual product was obtained. The explanation for its formation is that intended diene **104** was generated slowly, but underwent further reaction under the conditions of its formation. Further work aimed at the synthesis of **104** would

be worthwhile because of the possibility of performing *N*-alkylation reaction that would simultaneously introduce a dienophile and activate the diene towards IEDDA reaction.

The majority of the 2-hydroxybenzophenones synthesized under this transformation could conceivably serve as precursors to isophthalates¹⁷ and therefore be employed in cyclophane synthesis. For example 2-hydroxybenzophenone **81a** could be converted to diester **82** (Scheme 2.18). Diester **82** could then be converted into dithiacyclophanes **129** and **130**. Upon heating, cyclophane **129** could conceivably afford intermediate **131** which could undergo intramolecular [4+4] cycloaddition to afford **132**. Desulfurization of **132** could afford cyclophane **133**, which is a potential precursor to superphane (**134**). On the other hand, cyclophane **130** could be converted into cyclophanediene **135** and then pyrene **136**. Heating of pyrene **136** in the presence of suitable dienophiles would open the door to the synthesis of larger PAHs (Scheme 2.18).



Scheme 2.18 Proposed future work using compound **81a** for hydroxybenzophenones.

2.8 Experimental Section

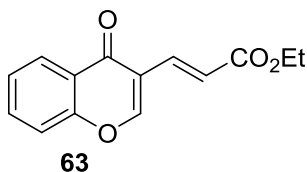
THF was dried by distillation over sodium metal and CH_2Cl_2 was distilled from calcium hydride under N_2 immediately prior to use. Piperidine and pyrrolidine were dried over KOH and distilled prior to use. All other reagents and starting materials were used as received. Flash silica gel was used for all column chromatography, particle size 40-60 μm . Compounds on tlc plates were visualised under UV light (254 and 365 nm).

NMR. Solutions of compounds for ^1H and ^{13}C NMR were prepared in the deuterated solvents specified. All ^1H and ^{13}C NMR spectra were acquired using a Bruker Avance 300 spectrometer. Data were processed and analysed using MestReNova software. ^1H NMR data are presented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (J), number of protons.

Mass Spectrometry. Mass spectrometry data was collected on an Agilent 1100 series LC/MSD chromatography system by flow injection analysis. Samples were dissolved in the solvent listed and ionized by atmospheric pressure chemical ionization (APCI) in either positive or negative mode.

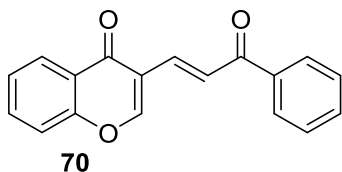
Melting Point. Melting points were collected using a Stanford Research Systems Optimelt automated melting point system with digital image processing Technology.

***E*-3-(2-(Ethoxycarbonyl)vinyl)-4*H*-chromen-4-one (63)**



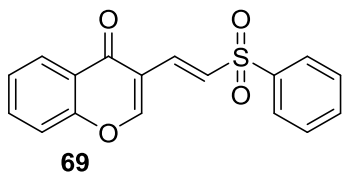
To a 0 °C suspension of NaH (2.08 g, 52.0 mmol) (60% dispersion in mineral oil) in THF (100 mL), was added triethyl phosphonoacetate (10.9 mL, 54.9 mmol) under N₂ and the resulting mixture was stirred for 1 h before being added by syringe to a solution of 3-formylchromone (6.00 g, 34.5 mmol) in THF (100 mL). The addition was accompanied by a colour change from colourless to bright yellow, then orange after a few minutes of stirring. After 48 h the starting material had been consumed (tlc analysis) at which point 1 M HCl solution (40 mL) was added. The majority of the organic solvent was removed by rotary evaporation; the aqueous mixture that was left was extracted with CH₂Cl₂ (4 × 20 mL). The combined organic layers were dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. Recrystallation of the residue from 95% ethanol gave compound **63** (6.40 g, 26.2 mmol, 74%) as a white solid. *R*_f (30% ethyl acetate/hexanes) = 0.36; mp = 108-109 °C; ¹H NMR (300 MHz, CDCl₃) δ = 8.28 (dd, *J* = 6.6, 1.7 Hz, 1H), 8.12 (s, 1H), 7.73-7.67 (m, 1H), 7.50-7.43 (m, 2H), 7.35 (q, *J* = 15.1 Hz, 2H), 4.26 (q, *J* = 7.1 Hz, 2H), 1.33 (t, *J* = 7.1 Hz, 3H); ¹³C NMR: (75 MHz, CDCl₃) δ = 175.91, 167.38, 157.30, 155.55, 135.32, 134.01, 126.37, 125.84, 124.24, 122.27, 199.38, 188.12, 60.51, 14.32; MS (APCI-(+), CH₂Cl₂): *m/z* (%) 246 (15), 245 (100, [M+1]⁺), 200 (10), 199 (60); HRMS (TOF-MS-APCI): Calc. for C₁₄H₁₂O₄: 244.0736, Found: 244.0740.

***E*-3-(2-Benzoylvinyl)-4*H*-chromen-4-one (70)**



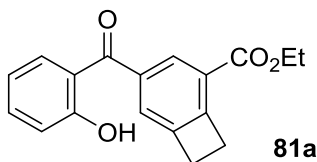
To a stirred slurry of NaH (1.71 g, 42.7 mmol) (60% dispersion in mineral oil) in THF (50 mL) at 0 °C was added triethylphosphonobenzophenone (10.9 g, 4.30 mmol) to give a colourless solution upon stirring. 3-formylchromone (6.20 g, 35.6 mmol) was dissolved in THF (125 mL) at 0 °C to give a clear yellow solution. The phosphonate carbanion was added dropwise to the 3-formylchromone solution, and the resulting solution was stirred overnight at room temperature. $\text{NH}_4\text{Cl}_{(\text{aq})}$ (35 mL) was added and the solution was stirred for 0.5 h. The solvent was removed under reduced pressure, and the resulting solid was dissolved in CH_2Cl_2 and washed with water (25 mL) and then $\text{NaHSO}_{3(\text{aq})}$ (4×10 mL). The solution was dried over MgSO_4 , and the solvent was removed under reduced pressure to yield, after chromatography R_f (2% ethyl acetate/dichloromethane) = 0.60, compound **70** as a yellow solid (6.90 g, 25.0 mmol, 70%). mp = 166-168 °C; ^1H NMR (300 MHz, CDCl_3) δ = 8.72 (d, J = 15.1 Hz, 1H), 8.34 (dd, J = 7.9, 1.1 Hz, 1 H), 8.24 (s, 1H), 8.16-8.13 (m, 2H), 7.79-7.72 (m, 1H), 7.65-7.48 (m, 6H). ^{13}C NMR: (75 MHz, CDCl_3) δ = 190.8, 176.6, 159.2, 155.6, 138.1, 135.6, 134.3, 133.2, 129.0, 128.9, 126.5, 126.2, 125.9, 124.5, 119.8, 118.4; MS (APCI-(+), CH_2Cl_2): m/z (%) 357 (100, $[\text{M}+1]^+$), 358 (25); HRMS (TOF-MS-APCI): Calc. for $\text{C}_{18}\text{H}_{12}\text{O}_3$: 276.0786, Found: 276.0788.

***E*-3-(2-(Phenylsulfonyl)vinyl)-4*H*-chromen-4-one (69)**¹⁷



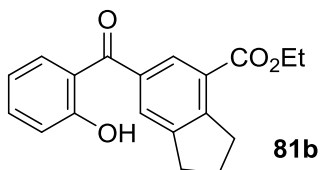
To stirred slurry of NaH (1.03 g, 25.8 mmol) (60% dispersion in oil) in THF (50 mL) was added sulfonephosphonate **78** (8.02 g, 28.9 mmol) to give a colourless solution. This solution was added dropwise to a solution of 3-formylchromone (3.00 g, 17.2 mmol) in THF (100 mL). The resulting solution was stirred at room temperature 48 h. The solvent was removed under reduced pressure through rotary evaporation. The product was purified by column chromatography (2% ethyl acetate/dichloromethane) to yield compound **73** (2.79 g, 9.80 mmol, 51%), as a white powder. m.p = 197-199 °C. ¹H NMR (300 MHz, CDCl₃) δ = 8.24 (dd, J = 7.8, 2.2 Hz, 1H), 8.20 (s, 1H), 8.12 (d, J = 15.1 Hz, 1H), 7.96 (td, J = 7.0, 1.9 Hz, 1H), 7.77-7.71 (m, 1H), 7.66-7.46 (m, 6H), 7.35 (d, J = 15.1 Hz, 1H); ¹³C NMR: (75 MHz, CDCl₃) δ = 175.71, 159.29, 155.45, 140.63, 134.43, 133.38, 133.11, 131.57, 129.33, 127.74, 126.24, 124.05, 118.26, 117.65; MS (APCI-+), CH₂Cl₂): m/z (%) 313 (100, [M+1]⁺), 314 (19); HRMS (TOF-MS-APCI): Calc. for C₁₇H₁₂O₄S: 312.0456, Found: 312.0457.

3-(Ethoxycarbonyl)-5-(2-hydroxybenzoyl)benzocyclobutene (**81a**)



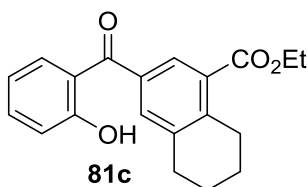
To a solution of diene **63** (2.51 g, 10.3 mmol) in CH₃CN (100 mL) was added cyclobutanone (1.29 g, 18.5 mmol), MgSO₄ (4.03 g, 33.5 mmol) and piperidine (0.44 g, 5.1 mmol). The mixture immediately turned bright orange upon addition of the amine and was stirred at room temperature for 18 h, at which point diene **63** was consumed totally (tlc analysis). The majority of the organic solvent was removed under reduced pressure and dichloromethane (40 mL) was added. The resulting reaction mixture was washed with 1 M HCl solution (4 × 10 mL) and the organic layer was dried over anhydrous MgSO₄, filtered and the solvent was removed under reduced pressure. The residue was subjected to column chromatography (3.5 × 15 cm, 20% ethyl acetate/hexane) to afford compound **81a** as a yellow solid (2.73 g, 9.20 mmol, 90%). *R_f* (30% ethyl acetate/hexane) = 0.48; mp = 60-62 °C; ¹H NMR (300 MHz, CDCl₃) δ = 11.96 (s, 1H), 8.10 (s, 1H), 7.56-7.48 (m, 3H), 7.09-7.05 (m, 1H), 6.88 (t, *J* = 8.1 Hz, 1H), 4.37 (q, *J* = 7.8 Hz, 2H), 3.50-3.29 (m, 4H), 1.39 (t, *J* = 7.1 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ = 201.16, 165.23, 163.24, 152.67, 146.57, 137.43, 136.39, 133.48, 129.09, 126.78, 125.12, 119.10, 118.78, 118.46, 60.99, 31.37, 29.88, 14.39; MS (APCI(-), CHCl₂): *m/z* (%) 296 (20), 295 (100, [M-1]); HRMS (TOF-MS-APCI): Calc. for C₁₈H₁₆O₄: 296.1047, Found: 296.1049.

6-(2-Hydroxybenzoyl)indan-4-carboxylic acid ethyl ester (81b)



To a solution of diene **63** (0.200 g, 0.820 mmol) in CH₃CN (8 mL) was added cyclopentanone (0.826 g, 9.82 mmol), MgSO₄ (0.250 g, 2.08 mmol) and piperidine (0.035 g, 0.410 mmol). The mixture immediately turned bright orange upon addition of the amine and was stirred at room temperature for 20 h, at which point diene **63** had been consumed (tlc analysis). The majority of the organic solvent was removed under reduced pressure and dichloromethane (40 mL) was added. The resulting reaction mixture was washed with 1 M HCl solution (4 × 10 mL) and the organic layer was dried over anhydrous MgSO₄, filtered and the solvent was removed under reduced pressure. The residue was subjected to column chromatography (3.5 × 13 cm, 20% ethyl acetate/hexane) to afford compound **81b** as a yellow solid (0.213 g, 0.691 mmol, 88%). *R_f* (30% ethyl acetate/hexane) = 0.70; mp = 95-96 °C; ¹H NMR (300 MHz, CDCl₃) δ = 11.96 (s, 1H), 8.14 (s, 1H), 7.70 (s, 1H), 7.60-7.50 (m, 2H), 7.10-7.09 (m, 1H), 6.92-6.89 (m, 1H), 4.42 (q, *J* = 7.1 Hz, 2H), 3.40 (t, *J* = 7.5 Hz, 2H), 2.22-2.12 (m, 2H) 1.41 (t, *J* = 7.1 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ = 201.100, 163.22, 146.57, 136.39, 133.44, 129.40, 128.52, 118.77, 118.46, 61.07, 34.15, 32.50, 25.03, 14.37; MS (APCI(-), CH₂Cl₂): *m/z* (%) 310 (18), 309 (100, [M-1]⁻); HRMS (TOF-MS-APCI): Calc. for C₁₉H₁₈O₄: 310.1205, Found: 310.1209.

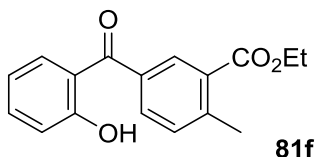
**5,6,7,8-Tetrahydro-3-(2-hydroxybenzoyl)naphthalene-1-carboxylic acid ethyl ester
(81c)**



To a solution of diene **63** (0.200 g, 0.820 mmol) in CH₃CN (8 mL) was added cyclohexanone (0.145 g, 1.48 mmol), MgSO₄ (0.250 g, 2.08 mmol) and piperidine (0.035 g, 0.410 mmol). The mixture immediately turned bright orange upon addition of the amine and was stirred at room temperature for 24 h, at which point diene **63** had been consumed (tlc analysis). The majority of the organic solvent was removed under reduced pressure and dichloromethane (40 mL) was added. The resulting reaction mixture was washed with 1 M HCl solution (4 × 10 mL) and the organic layer was dried over anhydrous MgSO₄, filtered and the solvent was removed under reduced pressure. The residue was subjected to column chromatography (3.5 × 13 cm, 20% ethyl acetate/hexane) to afford compound **81c** as a yellow solid (0.240 g, 0.740 mmol, 86%). *R_f* (30% ethyl acetate/hexane) = 0.60; mp = 48-50 °C); ¹H NMR (300 MHz, CDCl₃) δ = 11.96 (s, 1H), 7.95 (d, *J* = 1.8 Hz, 1H), 7.60 (dd, *J* = 6.3, 1.6 Hz, 1H), 7.57-7.49 (m, 2H), 7.09 (dd, *J* = 7.4, 1.0 Hz, 1H), 6.92-6.86 (m, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 3.14-3.12 (m, 2H), 2.89-2.87 (m, 2H) 1.38 (t, *J* = 7.1 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ = 201.72, 167.34, 163.20, 142.91, 138.93, 136.37, 134.74, 133.40, 133.88, 133.04, 128.47, 119.11, 118.46, 61.13, 30.29, 28.02, 24.46, 22.81, 22.23, 14.31; MS (APCI(-), CH₂Cl₂): *m/z* (%)

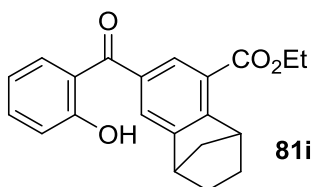
323 (100, [M-1]⁻), 389 (35), 324 (20), 390 (5); HRMS (TOF-MS-APCI): Calc, for C₂₀H₂₀O₄: 324.1362, Found: 324.1364.

3'-Carboxyethyl-4'-methyl-2-hydroxybenzophenone (81f)



To diene **63** (0.200 g, 0.820 mmol) in acetone (8 mL) was added MgSO_4 (0.250 g, 2.08 mmol) and piperidine (0.035 g, 0.410 mmol). The mixture immediately turned bright orange upon addition of the amine and was stirred at room temperature for 18 h, at which point diene **63** had been consumed (tlc analysis). The majority of the organic solvent was removed under reduced pressure and dichloromethane (40 mL) was added. The resulting reaction mixture was washed with 1 M HCl solution (4×10 mL) and the organic layer was dried over anhydrous MgSO_4 , filtered and the solvent was removed under reduced pressure. The residue was subjected to column chromatography (3.5×13 cm, 20% ethyl acetate/hexane) to afford compound **81f** as a yellow solid (0.186 g, 0.660 mmol, 81%). R_f (30% ethyl acetate/hexane) = 0.92; mp = 86-88 °C); ^1H NMR (300 MHz, CDCl_3) δ = 11.96 (s, 1H), 8.25 (d, J = 1.9 Hz, 1H), 7.73 (dd, J = 7.9, 1.9 Hz, 1H), 7.58-7.49 (m, 2H), 7.41 (d, J = 7.9 Hz, 1H), 7.10 (d, J = 0.8 Hz, 1H), 6.92-6.91 (m, 1H), 4.42 (q, J = 7.1 Hz, 2H), 2.70 (s, 3H), 1.42 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ = 200.40, 166.74, 163.23, 144.43, 136.48, 135.52, 130.23, 119.04, 118.53, 61.20, 50.58, 21.87, 14.32; MS (APCI(-), CH_2Cl_2): m/z (%) 284 (20, M^+), 283 (100); HRMS (TOF-MS-APCI): Calc. for $\text{C}_{17}\text{H}_{16}\text{O}_4$: 284.1049, Found: 284.1052.

(1*R,4*S**)-1,2,3,4-Tetrahydro-7-(2-hydroxybenzoyl)-1,4-methanonaphthalene-5-carboxylic acid ethyl ester (81i)**

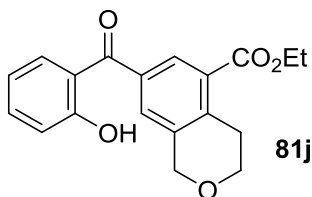


To a solution of diene **63** (0.200 g, 0.820 mmol) in CH₃CN (8 mL) was added norcamphor (0.162 g, 1.47 mmol), MgSO₄ (0.250 g, 2.08 mmol) and piperidine (0.035 g, 0.410 mmol). The mixture immediately turned bright orange upon addition of the amine and was stirred at room temperature for 32 h, at which point diene **63** had been consumed (tlc analysis). The majority of the organic solvent was removed under reduced pressure and dichloromethane (40 mL) was added. The resulting reaction mixture was washed with 1 M HCl solution (4 × 10 mL) and the organic layer was dried over anhydrous MgSO₄, filtered and the solvent was removed under reduced pressure. The residue was subjected to column chromatography (3.5 × 13 cm, 20% ethyl acetate/hexane) to afford compound **81i** as a yellow solid (0.177 g, 0.530 mmol, 65%). *R_f* (30% ethyl acetate/hexane) = 0.52; mp = 92-96 °C); ¹H NMR (300 MHz, CDCl₃) δ = 11.99 (s, 1H), 8.05 (s, 1H), 7.64-7.59 (m, 3H), 7.09-7.06 (m, 1H), 6.92-6.87 (m, 1H), 4.43 (q, *J* = 7.1, Hz, 2H), 4.27 (s, 1H), 3.47 (s, 1H), 2.09-1.95 (m, 2H), 1.84-1.80 (m, 1H) 1.64-1.55 (m, 3H), 1.43 (t, *J* = 7.2 Hz, 3H), 1.26-1.21 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ = 166.36, 163.20, 154.36, 150.20, 136.30, 135.41, 133.52, 128.78, 124.61, 123.59, 119.20, 118.73, 118.42, 61.06, 48.63, 43.71, 43.45, 26.64, 25.71, 14.37; MS (APCI(-), CH₂Cl₂): *m/z* (%)

= 336 (25), 335 (100, [M-1]⁻); HRMS (TOF-MS-APCI): Calc. for C₂₁H₂₂O₄: 336.1362,

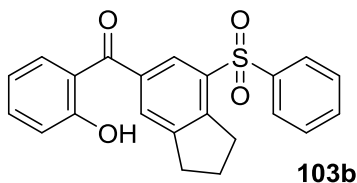
Found: 336.1374.

7-(2-Hydroxybenzoyl)isochroman-5-carboxylic acid ethyl ester (81j)



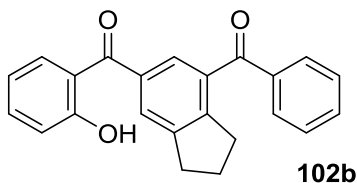
To a solution of diene **81j** (0.200 g, 0.820 mmol) in CH₃CN (8 mL) was added tetrahydro-4H-pyran-4-one (0.147 g, 1.47 mmol), MgSO₄ (0.250 g, 2.08 mmol) and piperidine (0.035 g, 0.410 mmol). The mixture immediately turned bright orange upon addition of the amine and was stirred at room temperature for 24 h, at which point diene **63** had been consumed (tlc analysis). The majority of the organic solvent was removed under reduced pressure and dichloromethane (40 mL) was added. The resulting reaction mixture was washed with 1 M HCl solution (4 × 10 mL) and the organic layer was dried over anhydrous MgSO₄, filtered and the solvent was removed under reduced pressure. The residue was subjected to column chromatography (3.5 × 13 cm, 20% ethyl acetate/hexane) to afford compound **81j** as a yellow solid (0.216 g, 0.620 mmol, 81%). *R_f* (30% ethyl acetate/hexane) = 0.51; mp = 65-66 °C); ¹H NMR (300 MHz, CDCl₃) δ = 11.89 (s, 1H), 8.14 (d, *J* = 1.8 Hz, 1H), 7.56-7.27 (m, 3H), 7.10-7.07 (m, 1H), 6.93-6.87 (m, 1H), 4.87 (s, 2H), 4.41 (q, *J* = 7.1 Hz, 2H), 4.03 (t, *J* = 5.8 Hz, 2H), 3.32 (t, *J* = 5.8, 2H), 1.41 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ = 166.36, 163.20, 154.36, 150.20, 136.30, 135.41, 133.52, 128.78, 124.61, 123.59, 119.20, 118.73, 118.42, 61.06, 48.63, 43.71, 43.45, 26.64, 25.71, 14.37; MS (APCI(-), CH₂Cl₂): *m/z* (%) = 325 (100, [M-1]⁻), 357 (60) 387 (45), 326 (20); HRMS (TOF-MS-APCI): Calc. for C₁₉H₁₈O₅: 326.1154, Found: 326.1165.

6-(2-Hydroxybenzoyl)-4-(phenylsulfonyl)indan (103b)



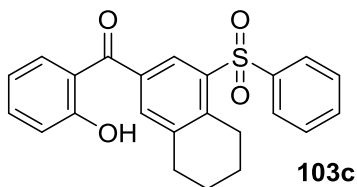
To a solution of diene **69** (0.200 g, 0.640 mmol) in CH₃CN (8 mL) was added cyclopentanone (0.046 g, 0.540 mmol), MgSO₄ (0.250 g, 2.08 mmol) and piperidine (0.014 g, 0.16 mmol). The mixture immediately turned bright orange upon addition of the amine and was stirred at room temperature for 20 h, at which point diene **69** had been consumed (tlc analysis). The majority of the organic solvent was removed under reduced pressure and dichloromethane (40 mL) was added. The resulting reaction mixture was washed with 1 M HCl solution (4 × 10 mL) and the organic layer was dried over anhydrous MgSO₄, filtered and the solvent was removed under reduced pressure. The residue was subjected to column chromatography (3.5 × 13 cm, 30% ethyl acetate/hexane) to afford compound **103a** as a yellow solid (0.232 g, 0.610 mmol, 95%). *R_f* (30% ethyl acetate/hexane) = 0.47; mp = 146-148 °C; ¹H NMR (300 MHz, CDCl₃) δ = 11.93 (s, 1H), 7.83-7.79 (m, 1H), 7.79 (d, *J* = 1.5 Hz, 1H), 7.71 (s, 1H), 7.62-7.55 (m, 3H), 7.52-7.43 (m, 3H), 7.04 (dd, *J* = 8.4, 0.9 Hz, 1H), 6.86 (ddd, *J* = 8.2, 7.2, 1.1 Hz, 1H), 3.15-3.00 (m, 4H), 2.22-2.09 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ = 199.98, 163.30, 148.78, 148.24, 147.69, 136.84, 135.51, 133.22, 129.28, 127.47, 119.08, 118.89, 118.65, 32.63, 32.44, 24.98; MS (APCI(+), CH₂Cl₂): *m/z* (%) = 378 (65), 237 (45), 121 (100), 115 (21); HRMS (TOF-MS-APCI): Calc. for C₂₂H₁₈O₄S: 378.0900, Found: 378.0919.

4-Benzoyl-6-(2-hydroxybenzoyl)indan (**102b**)



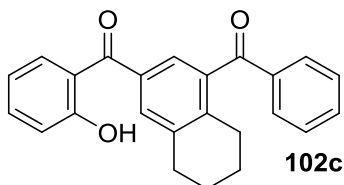
To a solution of diene **70** (0.200 g, 0.720 mmol) in CH₃CN (8 mL) was added cyclopentanone (0.052 g, 0.61 mmol), MgSO₄ (0.250 g, 2.08 mmol) and piperidine (0.015 g, 0.18 mmol). The mixture immediately turned bright orange upon addition of the amine and was stirred at room temperature for 20 h, at which point diene **70** had been consumed (tlc analysis). The majority of the organic solvent was removed under reduced pressure and dichloromethane (40 mL) was added. The resulting reaction mixture was washed with 1 M HCl solution (4 × 10 mL) and the organic layer was dried over anhydrous MgSO₄, filtered and the solvent was removed under reduced pressure. The residue was subjected to column chromatography (3.5 × 13 cm, 30% ethyl acetate/hexane) to afford compound **103b** as a yellow solid (0.205 g, 0.600 mmol, 83%). *R_f* (30% ethyl acetate/hexane) = 0.69; mp = 170-172 °C; ¹H NMR (300 MHz, CDCl₃) δ = 11.97 (s, 1H), 7.94-7.81 (m, 2H), 7.74 (s, 1H), 7.63-7.46 (m, 6H), 7.06 (d, *J* = 7.2, 1H), 6.90-6.85 (m, 1H), 3.14-3.03 (m, 4H), 2.22-2.12 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ = 201.1, 197.0, 163.3, 149.6, 146.7, 137.5, 136.6, 136.0, 134.4, 133.5, 130.1, 128.9, 128.7, 127.8, 119.2, 118.9, 118.6, 33.0, 32.7, 25.6; MS (APCI(+), CH₂Cl₂): *m/z* (%) = 342 (100), 121 (88), 237 (48), 105 (42), 77 (35); HRMS (TOF-MS-APCI): Calc. for C₂₃H₁₈O₃: 342.1262, Found: 342.1264.

5,6,7,8-Tetrahydro-3-(2-hydroxybenzoyl)-1-(phenylsulfonyl)naphthalene (103c)



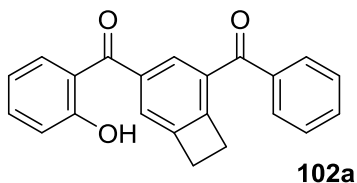
To a solution of diene **69** (0.200 g, 0.640 mmol) in CH₃CN (8 mL) was added cyclohexanone (0.054 g, 0.55 mmol), MgSO₄ (0.250 g, 2.08 mmol) and piperidine (0.014 g, 0.16 mmol). The mixture immediately turned bright orange upon addition of the amine and was stirred at room temperature for 24 h, at which point diene **69** had been consumed (tlc analysis). The majority of the organic solvent was removed under reduced pressure and dichloromethane (40 mL) was added. The resulting reaction mixture was washed with 1 M HCl solution (4 × 10 mL) and the organic layer was dried over anhydrous MgSO₄, filtered and the solvent was removed under reduced pressure. The residue was subjected to column chromatography (3.5 × 13 cm, 30% ethyl acetate/hexane) to afford compound **103c** as a yellow solid (0.206 g, 0.530 mmol, 80%). *R_f* (30% ethyl acetate/hexane) = 0.60 ; mp = 170-172 °C; ¹H NMR (300 MHz, CDCl₃) δ = 11.90 (s, 1H), 8.37 (d, *J* = 2.3 Hz, 1H), 7.90-7.87 (m, 2H), 7.65-7.52 (m, 6H), 7.12-7.09 (m, 1H), 6.96-6.91 (m, 1H), 3.03 (s, 2H), 2.90 (s, 2H), 1.83-1.73 (m, 4H); ¹³C NMR (75 MHz, CDCl₃) δ = 199.9, 1.63.4, 141.4, 140.7, 139.2, 137.0, 135.4, 135.1, 133.5, 133.3, 129.3, 128.0, 127.9, 119.2, 118.9, 188.7, 30.3, 26.7, 22.2, 21.8; MS (APCI(+), CH₂Cl₂): *m/z* (%) = 392 (30), 251 (32), 121 (100); HRMS (TOF-MS-APCI): Calc. for C₂₃H₂₀O₄S: 392.1077, Found: 392.1079.

1-Benzoyl-5,6,7,8-tetrahydro-3-(2-hydroxybenzoyl)naphthalene (102c)



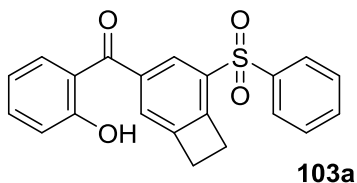
To a solution of diene **70** (0.200 g, 0.720 mmol) in CH₃CN (8 mL) was added cyclohexanone (0.060 g, 0.61 mmol), MgSO₄ (0.250 g, 2.08 mmol) and piperidine (0.015 g, 0.18 mmol). The mixture immediately turned bright orange upon addition of the amine and was stirred at room temperature for 24 h, at which point diene **70** had been consumed (tlc analysis). The majority of the organic solvent was removed under reduced pressure and dichloromethane (40 mL) was added. The resulting reaction mixture was washed with 1 M HCl solution (4 × 10 mL) and the organic layer was dried over anhydrous MgSO₄, filtered and the solvent was removed under reduced pressure. The residue was subjected to column chromatography (3.5 × 13 cm, 30% ethyl acetate/hexane) to afford compound **102c** as a yellow solid (0.222 g, 0.620 mmol, 86%). *R_f* (30% ethyl acetate/hexane) = 0.68 ; mp = 48-50 °C; ¹H NMR (300 MHz, CDCl₃) δ = 11.97 (s, 1H), 7.87-7.83 (m, 2H), 7.65-7.47 (m, 6H), 7.41 (d, *J* = 2.2 Hz, 1H), 7.07 (dd, *J* = 8.5, 1.1 Hz, 1H), 6.91-6.85 (m, 1H), 2.95 (t, *J* = 6.3 Hz, 2H), 2.81 (t, *J* = 6.2 Hz, 2H) 1.91-1.79 (m, 4H); ¹³C NMR (75 MHz, CDCl₃) δ = 200.9, 198.1, 163.3, 140.1, 139.1, 138.9, 137.1, 136.5, 134.7, 133.8, 133.5, 131.7, 130.2, 128.8, 126.0, 119.2, 118.9, 118.5, 30.0, 27.5, 22.7, 22.5; MS (APCI-(+), CH₂Cl₂): *m/z* (%) = 357 (100, [M+1]⁺), 358 (25); HRMS (TOF-MS-APCI): Calc. for C₂₄H₂₀O₃: 356.1407, Found: 356.1412.

3-Benzoyl-5-(2-hydroxybenzoyl)benzocyclobutene (**102a**)



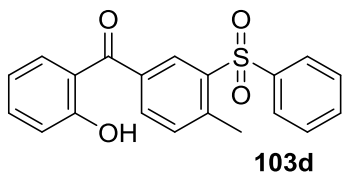
To a solution of diene **70** (0.200 g, 0.720 mmol) in CH₃CN (8 mL) was added cyclobutanone (0.043 g, 0.62 mmol), MgSO₄ (0.205 g, 2.08 mmol) and piperidine (0.015 g, 0.18 mmol). The mixture immediately turned bright orange upon addition of the amine and was stirred at room temperature for 18 h, at which point diene **70** had been consumed (tlc analysis). The majority of the organic solvent was removed under reduced pressure and dichloromethane (40 mL) was added. The resulting reaction mixture was washed with 1 M HCl solution (4 × 10 mL) and the organic layer was dried over anhydrous MgSO₄, filtered and the solvent was removed under reduced pressure. The residue was subjected to column chromatography (3.5 × 13 cm, 30% ethyl acetate/hexane) to afford compound **102a** as a yellow solid (0.230 g, 0.700 mmol, 96%). *R_f* (30% ethyl acetate/hexane) = 0.67; mp = 105-107 °C; ¹H NMR (300 MHz, CDCl₃) δ = 11.96 (s, 1H), 7.90 (s, 1H), 7.85-7.82 (m, 2H), 7.69-7.47 (m, 6H), 7.07 (m, 1H), 6.91-6.86 (m, 1H), 3.32-3.25 (m, 4H); ¹³C NMR (75 MHz, CDCl₃) δ = 210.17, 163.27, 154.93, 151.28, 146.77, 136.48, 133.47, 132.90, 129.59, 129.36, 128.55, 126.40, 119.09, 118.79, 118.52, 31.25, 29.76; MS (APCI(+), CH₂Cl₂): *m/z* (%) = 328 (95), 121 (100), 299 (65), 77 (58), 223 (55); HRMS (TOF-MS-APCI): Calc. for C₂₂H₁₆O₃: 328.1100, Found: 328.1103.

3-phenylsulfonyl-5-(2-hydroxybenzoyl)benzocyclobutene (**103a**)



To a solution of diene **69** (0.200 g, 0.640 mmol) in CH₃CN (8 mL) was added cyclobutanone (0.039 g, 0.55 mmol), MgSO₄ (0.250 g, 2.08 mmol) and piperidine (0.014 g, 0.16 mmol). The mixture immediately turned bright orange upon addition of the amine and was stirred at room temperature for 18 h, at which point diene **69** had been consumed (tlc analysis). The majority of the organic solvent was removed under reduced pressure and dichloromethane (40 mL) was added. The resulting reaction mixture was washed with 1 M HCl solution (4 × 10 mL) and the organic layer was dried over anhydrous MgSO₄, filtered and the solvent was removed under reduced pressure. The residue was subjected to column chromatography (3.5 × 13 cm, 30% ethyl acetate/hexane) to afford compound **103a** as a yellow solid (0.192 g, 0.530 mmol, 82%). *R_f* (30% ethyl acetate/hexane) = 0.54; mp = 191-193 °C; ¹H NMR (300 MHz, CDCl₃) δ = 11.80 (s, 1H), 8.03-7.94 (m, 3H), 7.67-7.48 (m, 5H), 7.45 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.08 (dd, *J* = 8.4, 0.8 Hz, 1H), 6.88 (ddd, *J* = 8.2, 7.2, 1.1 Hz, 1H), 3.46-3.40 (m, 2H), 3.35 -3.29 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ = 200.10, 163.33, 149.22, 147.81, 136.83, 133.70, 133.25, 129.45, 127.77, 127.57, 126.65, 119.02, 118.79, 118.66, 30.49, 30.45; MS (APCI(+), CH₂Cl₂): *m/z* (%) = 364 (45), 299 (65), 121 (100); HRMS (TOF-MS-APCI): Calc. for C₂₁H₁₆O₄S: 364.0800 Found: 364.0802.

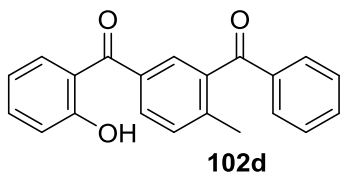
4-(2-hydroxybenzoyl)- 2-(phenylsulfonyl)toulene (103d)



To a solution of diene **69** (0.200 g, 0.640 mmol) in acetone (8 mL) was added MgSO_4 (0.250 g, 2.08 mmol) and piperidine (0.014 g, 0.16 mmol). The mixture immediately turned bright orange upon addition of the amine and was stirred at room temperature for 18 h, at which point diene **69** had been consumed (tlc analysis). The majority of the organic solvent was removed under reduced pressure and dichloromethane (40 mL) was added. The resulting reaction mixture was washed with 1 M HCl solution (4×10 mL) and the organic layer was dried over anhydrous MgSO_4 , filtered and the solvent was removed under reduced pressure. The residue was subjected to column chromatography (3.5 x 13 cm, 30% ethyl acetate/hexane) to afford compound **103d** as a yellow solid (0.192 g, 0.530 mmol, 83%). R_f (30% ethyl acetate/hexane) = 0.54; mp = 152-153 °C; ^1H NMR (300 MHz, CDCl_3) δ = 11.84 (s, 1H), 8.52 (d, J = 1.9 Hz, 1H), 7.94-7.87 (m, 2H), 7.81 (dd, J = 7.8, 1.8 Hz, 1H), 7.66-7.49 (m, 5H), 7.40 (d, J = 7.9 Hz, 1H), 7.11-7.06 (m, 1H), 6.92 (ddd, J = 8.2, 6.0, 1.1 Hz, 1H), 2.56 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ = 199.45, 163.35, 142.12, 140.58, 139.50, 136.93, 136.33, 133.81, 133.51, 133.10, 133.05, 130.21, 129.27, 127.90, 119.13, 118.77, 118.72, 20.45; MS (APCI-+), CH_2Cl_2): m/z (%)

= 352 (58), 337 (65), 121 (100); HRMS (TOF-MS-APCI): Calc. for $C_{20}H_{16}O_4S$:
352.0800, Found: 352.0802.

2-Benzoyl-4-(2-hydroxybenzoyl)toluene (102d)



To a solution of diene **70** (0.200 g, 0.720 mmol) in acetone (8 mL) was added MgSO_4 (0.250 g, 2.08 mmol) and piperidine (0.015 g, 0.18 mmol). The mixture immediately turned bright orange upon addition of the amine and was stirred at room temperature for 18 h, at which point diene **70** had been consumed (tlc analysis). The majority of the organic solvent was removed under reduced pressure and dichloromethane (40 mL) was added. The resulting reaction mixture was washed with 1 M HCl solution (4×10 mL) and the organic layer was dried over anhydrous MgSO_4 , filtered and the solvent was removed under reduced pressure. The residue was subjected to column chromatography (3.5×13 cm, 30% ethyl acetate/hexane) to afford compound **102d** as a yellow solid (0.200 g, 0.630 mmol, 87%). R_f (30% ethyl acetate/hexane) = 0.64; ^1H NMR (300 MHz, CDCl_3) δ = 11.90 (s, 1H), 7.81 (m, 2H), 7.73 (dd, J = 7.9, 1.8 Hz, 1H), 7.64 (d, J = 1.8 Hz, 1H), 7.62-7.57 (m, 2H), 7.52-7.42 (m, 4H), 7.05 (dd, J = 8.4, 0.8 Hz, 1H), 6.85 (ddd, J = 8.3, 7.3, 1.2 Hz, 1H), 2.43 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ = 200.40, 197.40, 163.21, 141.34, 138.79, 137.06, 136.50, 135.09, 133.70, 133.32, 131.21, 130.87, 130.16, 129.14, 128.73, 119.02, 118.81, 118.52, 20.16; MS (APCI-(+), CH_2Cl_2): m/z (%) = 315 (49, $[\text{M}+1]^+$), 316 (90), 121 (100), 105 (45), HRMS (TOF-MS-APCI): Calc. for $\text{C}_{21}\text{H}_{16}\text{O}_3$: 316.1101, found, 316.1103.

2.9 References

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3.0 Chapter 3

3.1 Cyclophanes

Cyclophanes are hydrocarbons consisting of an aromatic unit (most commonly a benzene ring) and an aliphatic chain that forms a bridge between two non-adjacent positions of the aromatic ring.¹ Cyclophanes have attracted broad interest from the organic chemistry community for several decades due to their interesting and unusual structures, strain, symmetry, synthetic challenge, conformational behaviour and physical properties. It is still an interesting field of research, which now overlaps with areas such as asymmetric synthesis, supramolecular chemistry and materials science.²

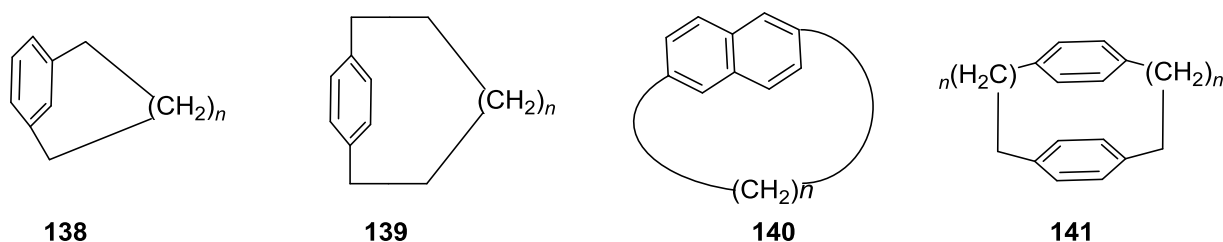


Figure 3.1 Skeletal structures of some simple and complex cyclophanes.

Compounds **138** and **139** are among the simplest of cyclophanes because they consist of an aromatic system in which two non-adjacent atoms on this system are connected by an aliphatic bridge. When the aromatic system is benzene, the prefixes meta- and para- are used to indicate relationship of the carbon atoms that are bridged. For larger aromatic systems, two numbers that correspond to the numbering of the arene are used in parentheses. The number of atoms in the bridge is placed in the brackets and they

are denoted by $[n]$. Thus, compound **140** is a $[n](2,6)$ naphthalenophanes. Cyclophanes can have any number and type of aromatic systems and as many bridges as permitted by the aromatic units. Accordingly there is enormous structural scope and a specialized system of nomenclature has been developed.³ Examples of multibridged **142**, heteroaromatic (**143**, **146**), non-benzenoid **144** and polycyclic aromatic hydrocarbons **145** are shown in figure 3.2.

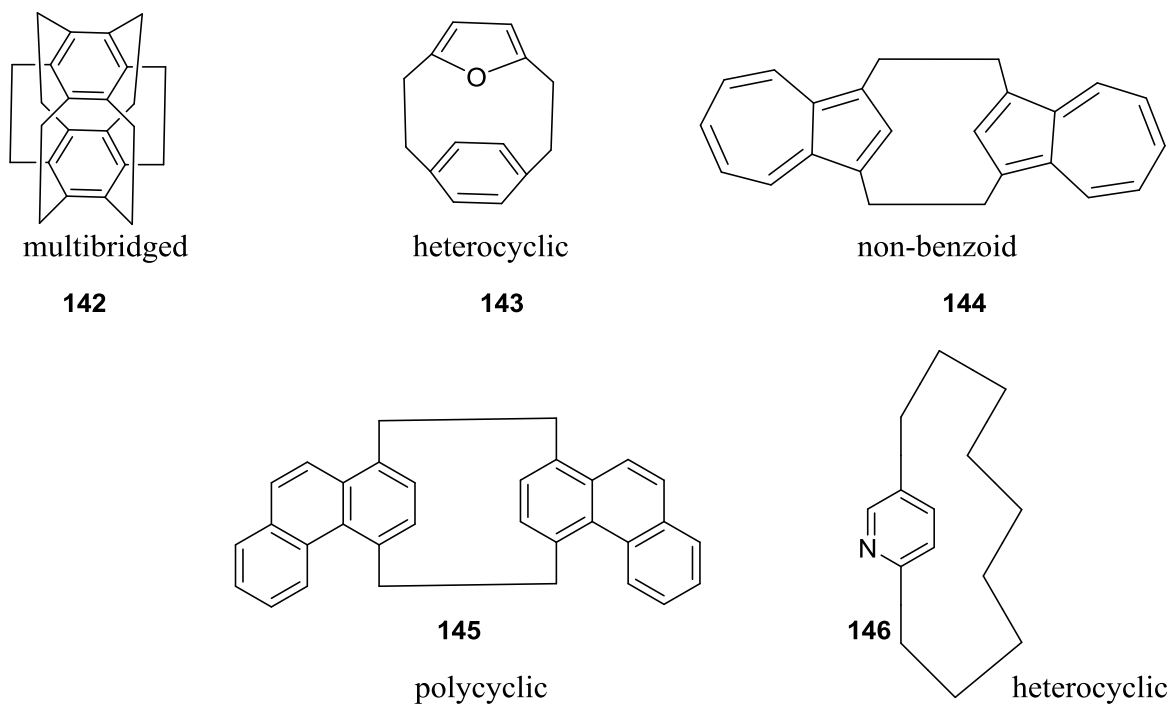
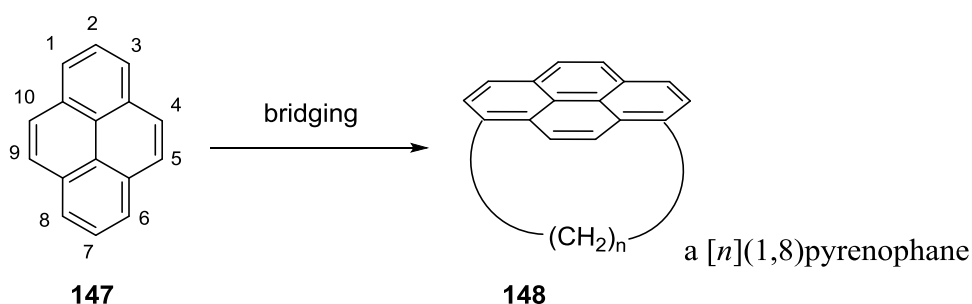


Figure 3.2 Structures of several simple cyclophanes.

3.2 Pyrenophanes

When the aromatic system in a cyclophane is pyrene, the cyclophane is called a pyrenophane (Scheme 3.1). Pyrenophanes are interesting because of the nature of the aromatic system.

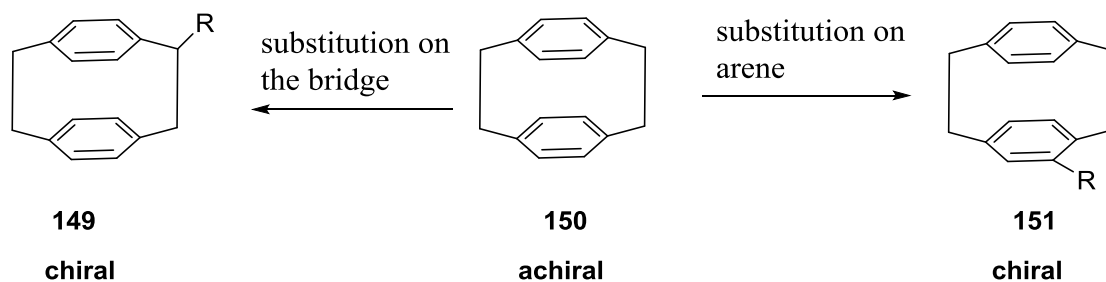


Scheme 3.1 Simple pyrenophane from one pyrene unit.

Pyrene is the smallest *peri*-fused polycyclic aromatic hydrocarbon and the largest polycyclic aromatic hydrocarbon to have been incorporated into a cyclophane on anything more than a sporadic basis.⁴ Pyrene is a compact polycyclic aromatic unit which has been widely exploited due to its electronic and photophysical properties as well as its ability to take part in non-covalent interactions. As such, it has been used as a key structural unit in organic materials^{5,6} that have been used in organic electronic devices, such as field effect transistors⁷ and supramolecular fluorescent sensors.⁸ The sensitivity of pyrene's fluorescence to its environment makes it a very effective fluorescent probe in a wide variety of systems. In fact, this property has elevated pyrene to "the status of gold standard as a molecular probe of microenvironments."⁴

Pyrene has also been employed in biological chemistry, especially in systems for binding nucleic acids⁹ and in the design of synthetic receptors for aromatic¹⁰ and carbohydrate¹¹ substrates. The pyrene unit is also valued for its binding properties. Having a large aromatic surface, it is capable of taking part in π -stacking and CH- π interactions which can be reinforced by the hydrophobic effect in water. This property of pyrene has been exploited frequently in the non-covalent functionalization of extended planar and non-planar π -systems such as carbon nanotubes and graphene.¹² Pyrene and its derivatives have found applications in diverse areas, including plastics, dyes, pesticides, pharmaceuticals, electroluminescent devices and others.¹³

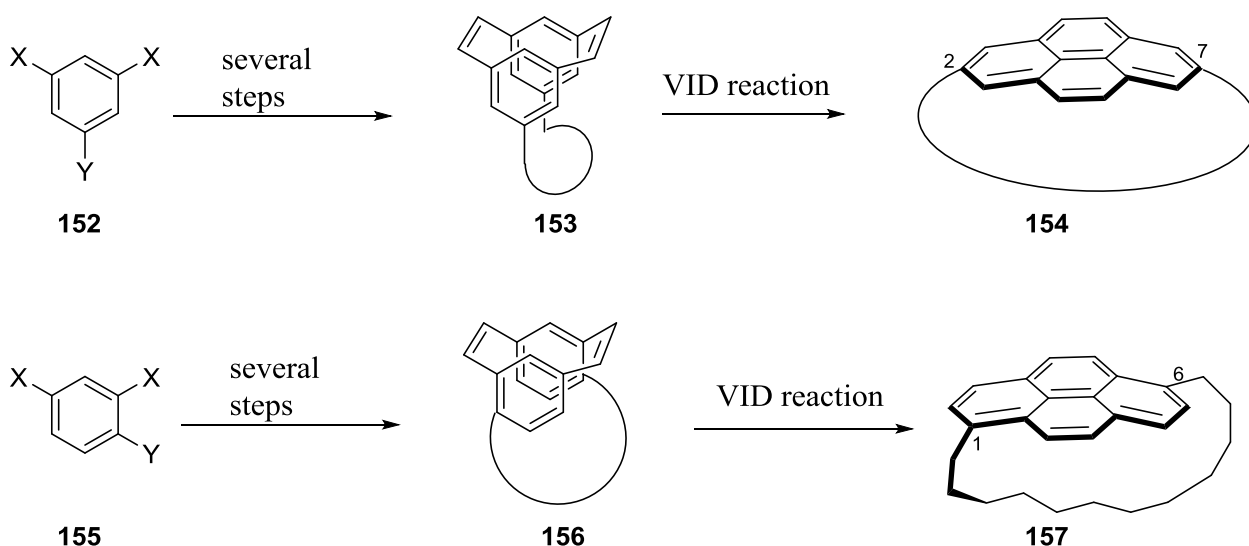
Chirality is an important aspect of cyclophane chemistry. Briefly, a parent cyclophane (one consisting of just aromatic units and bridges) can be chiral or achiral. Most of the typical well-known cyclophanes are achiral, e.g. [2.2]paracyclophanes (**150**). However, the introduction of a single substitute on either the bridge or the aromatic unit affords a chiral product (**149** or **151**) (Scheme 3.2).¹⁴



Scheme 3.2 Substitution of an inherently achiral cyclophane to give chiral cyclophane.

As far as pyrenophanes are concerned $[n](2,7)$ pyrenophanes **154** are inherently achiral, whereas the (1,6)Pyrenophanes **157** are inherently chiral. This means that they contain a chiral chromophore, which makes them interesting from the viewpoint of chiroptical properties.

Several $[n](2,7)$ pyrenophanes have been synthesized using a common strategy that starts with a 1,3,5-trisubstituted benzene. On the other hand only one simple $[n](1,6)$ pyrenophane has ever been synthesized. This was accomplished using the same strategy, but with a 1,2,4-trisubstituted starting material. However, the synthesis was very problematic. $[n](1,6)$ Pyrenophane **157** is C_2 -symmetric and chiral. Instead of just an end-to-end bend, which is present in pyrenophane **154**, the bridge of the $[n](1,6)$ pyrenophane **157** causes a longitudinal twist, or torsion, around the long axis of the pyrene system. The enantiomers of **157** were separated, which allowed the chiroptical and photophysical properties of the chiral pyrene system to be studied. Unfortunately, other $[n](1,6)$ pyrenophanes could not be synthesized using this strategy, so the changes in the chiroptical properties with increasing twist could not be evaluated.



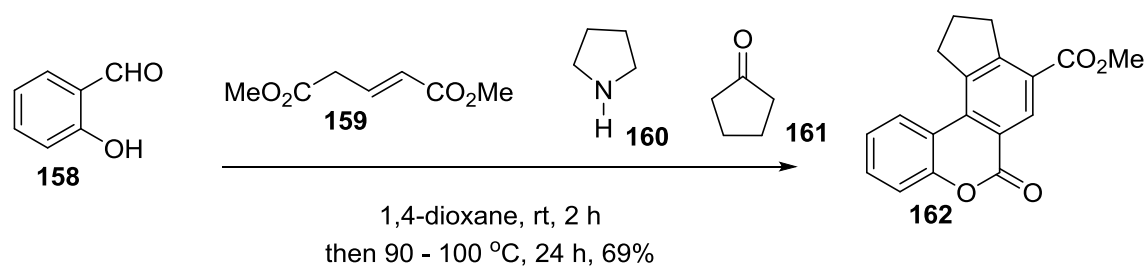
Scheme 3.3 Synthetic approach to $[n](2,7)$ pyrenophane **154** (achiral) and $[n](1,6)$ pyrenophane **157** (chiral). VID = valence isomerisation/dehydrogenation

A much more complex $[n](1,6)$ pyrenophane was recently reported by the Bodwell group.¹⁴ The synthetic approach differs greatly from the one used to synthesize **154** and **157** and evolved from the work aimed at the development of IEDDA-based multicomponent reactions (MCR).

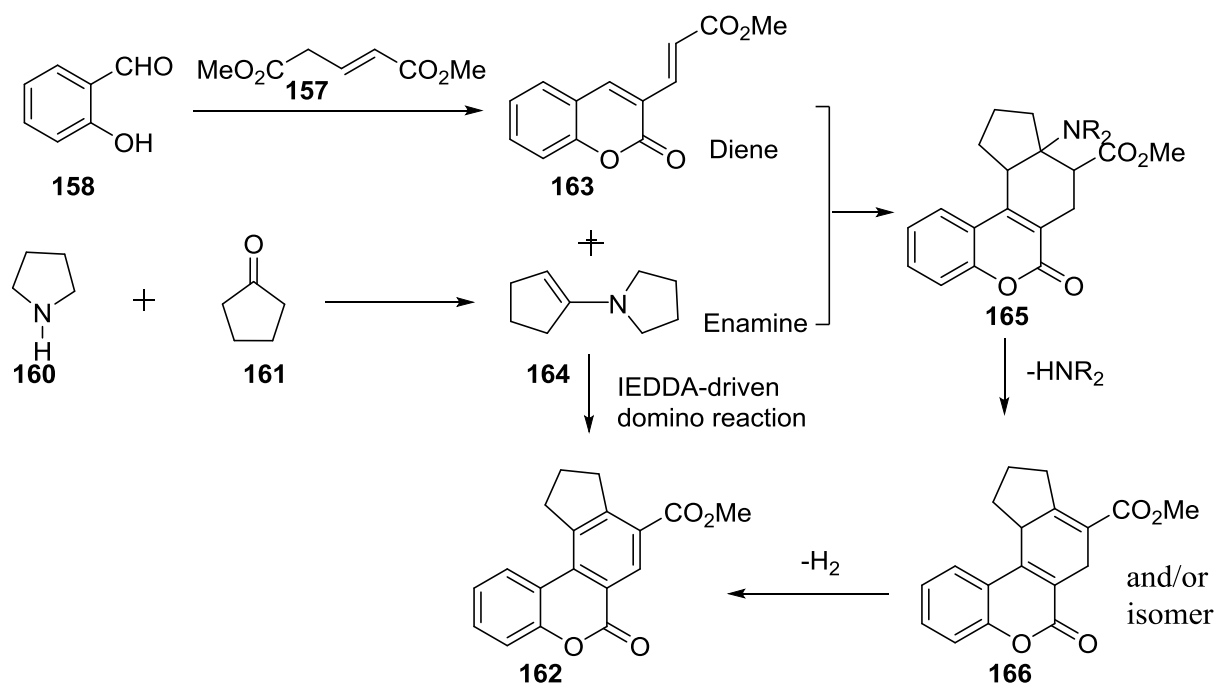
3.3 Multicomponent reaction

Multicomponent reactions are highly valuable reactions in chemistry due to their ability to incorporate three or more substrates into a single target in one synthetic operation.¹⁵ These reactions are very useful in synthetic chemistry for drug discovery, as well as in the total synthesis of natural products.¹⁷ The MCR that was developed by the Bodwell group affords (6*H*-dibenzo[*b,d*]pyran-6-ones (DBP). For example the reaction of

salicylaldehyde (**158**), dimethylglutaconate (**159**) and cyclopentanone (**161**) in the presence of pyrrolidine (**160**) in 1,4-dioxane afforded DBP **162** in 69% yield. In this reaction, six different reactions occur, including Knoevenagel condensation, transesterification, enamine formation, an inverse electron demand Diels-Alder (IEDDA) reaction, 1,2-elimination and transfer hydrogenation. An important feature of this reaction is that the secondary amine plays a catalytic function in both the formation of the electron deficient diene (Knoevenagel condensation) and the electron-rich dienophile (enamine)¹⁶ (Scheme 3.4).



One-pot synthesis of DBP

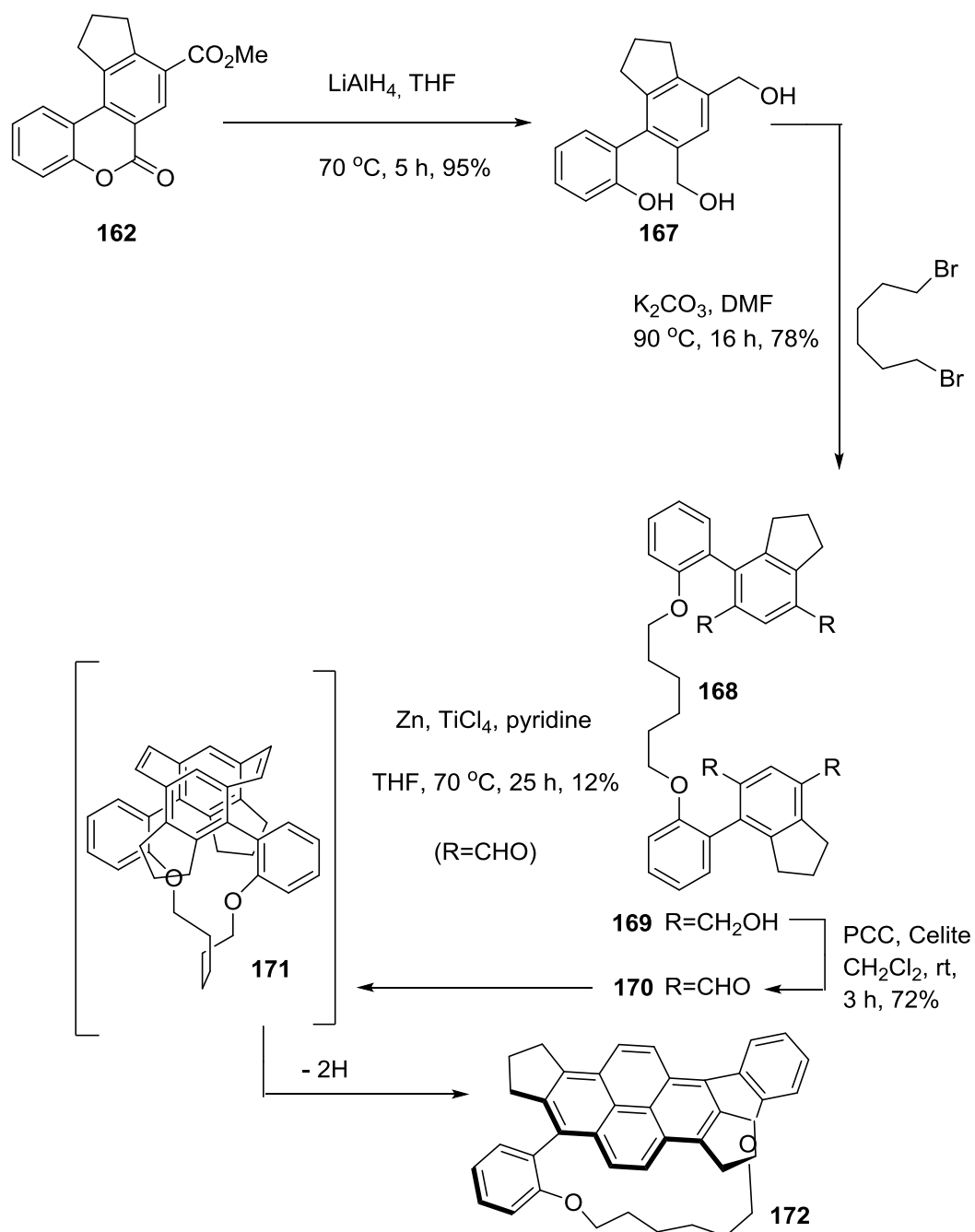


Scheme 3.4 Multicomponent reaction leading to DBP **162**.

The application of DBP **162** in the synthesis of pyrenophanes came from the identification of a suitable 1,2,4-trisubstituted benzene system in **162** (cf. **155**). This subunit became more obvious after the reduction of compound **162** with LiAlH_4 , which afforded triol **167** in 95% yield (Scheme 3.5). The two hydroxymethyl groups corresponding to “X” groups in **155** and the 2-hydroxymethyl group corresponding to the

“Y” substituent. The difference in acidities of the different types of (OH) groups (pK_a of phenol = 9.95; pK_a of benzyl alcohol = 15.40)¹⁷ enabled two units of **167** to be tethered. Thus reaction of **167** with 1,6-dibromohexane in the presence of potassium carbonate afforded tetraol **169** in 78% yield.

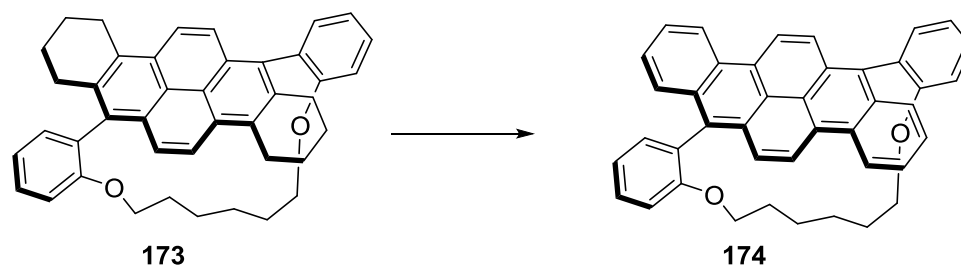
After attempts to convert **167** into the corresponding dithiacyclophane failed, tetraol **169** was oxidized with PCC/Celite to afford tetraldehyde **170** in 72% yield. When compound **170** was subjected to McMurry reaction conditions,¹⁸ [12](1,6)pyrenophane derivative **172** was obtained in 12% yield. The formation of **172** was quite surprising because the desired product was cyclophanediene **171**. Presumably, **171** did form, but underwent valence isomerization and dehydrogenation under the conditions of its formation. This very productive step brought about the formation of three new carbon-carbon bonds and two aromatic rings. Overall, the synthesis of **172** required only five steps from commercially available compounds, which is several steps less than the standard pyrenophane synthesis.



Scheme 3.5 Synthesis of (1,6)pyrenophane (**172**).

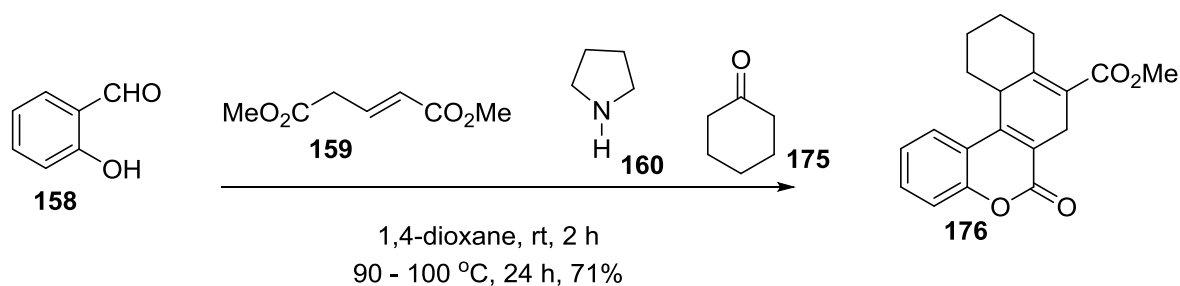
The objective of the work described in this chapter was to use the synthetic approach that was employed in the synthesis of **172** for the related pyrenophane **173**. The presence of six-membered rings was intended to allow for the formation of

dibenzo[*a,h*]pyrenophane **174**(Scheme 3.6). The larger PAH makes this a more interesting chiral chromophore and fluorophore than pyrene.



Scheme 3.6 Potential application of (1,6)pyrenophane **173**.

It was expected that the synthesis of **173** could be accomplished by replacing cyclopentanone with cyclohexanone in the initial MCR. Thus the reaction of salicylaldehyde (**158**), dimethylglutaconate (**159**), cyclohexanone **175** in the presence of pyrrolidine afforded diene **176** in 71% yield (Scheme 3.7).

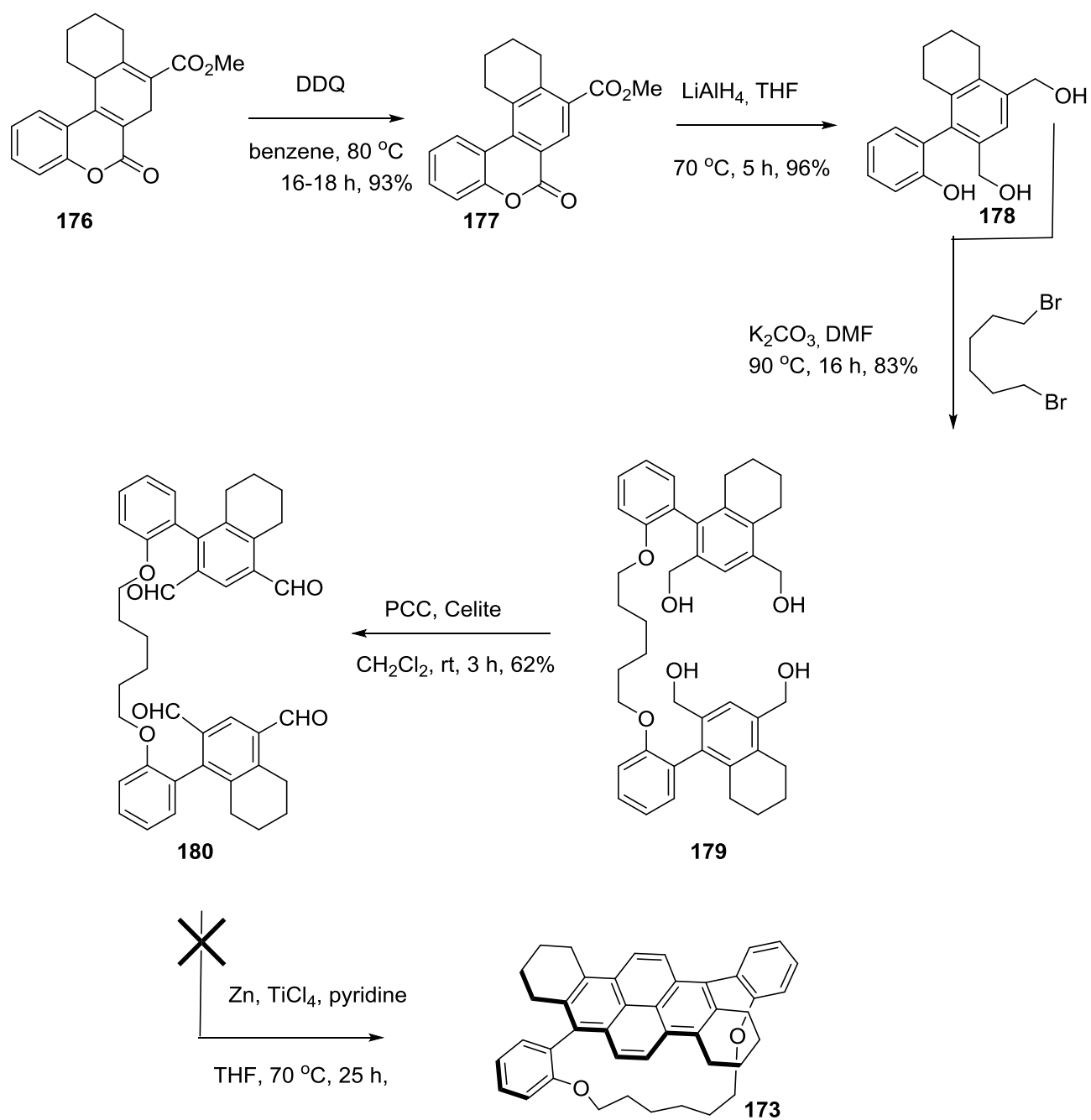


One pot synthesis of DBP with six-membered ring fused

Scheme 3.7 Multicomponent synthesis of 6*H*-dibenzo[*b,d*]pyran-6-one (DBP).

In this case, the dehydrogenation (transfer hydrogenation) step of the MCR did not take place. This may be due to the presence of steric strain across the *cove* region of the aromatized product **177** (Scheme 3.8). The incomplete MCR was not a problem

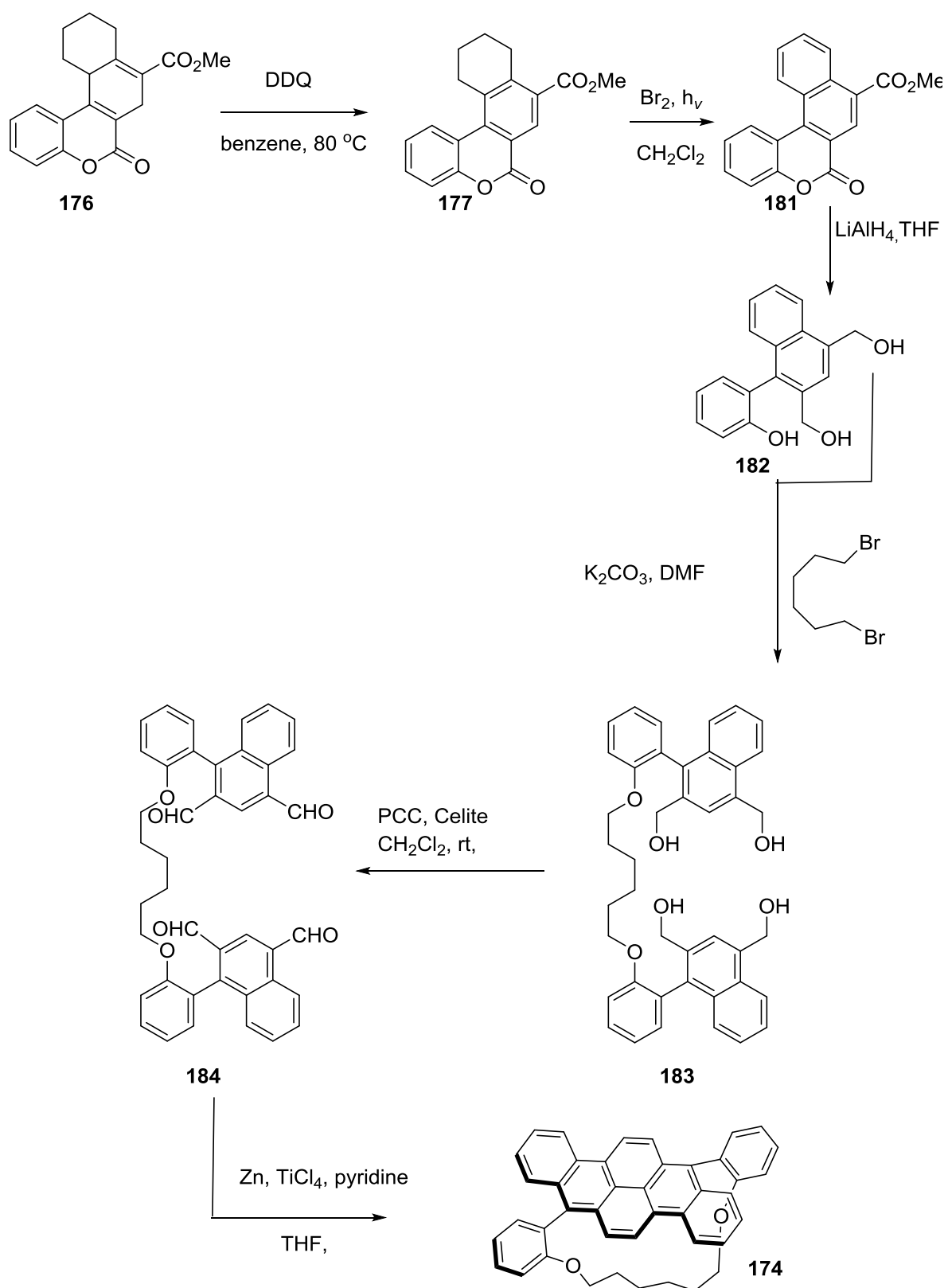
because aromatization of compound **176** to compound **177** could be achieved using DDQ in 93% yield. Reduction of compound **177** with LiAlH_4 then afforded triol **178** in 96% yield. Selective O-alkylation of the phenolic OH group with 1,6-dibromohexane afforded tetraol **179** in 83% yield. Tetraol **179** was oxidised to tetraldehyde **180** in 62% yield using PCC/Celite, which set the stage for the key cyclophane-forming McMurry reaction.¹⁸ Unfortunately, all attempts to synthesize pyrenophane **173** met with failure. In all cases, the starting material **180** was fully consumed, but none of the desired product was formed. The reason for the failure of this reaction is not obvious.



Scheme 3.8 Attempted synthesis of (1,6)pyrenophane **173**.

3.4 Future work

The synthesis of chiral pyrenophane **174** could also be tried by aromatizing the partially saturated six-membered ring directly following the multicomponent synthesis of the 6*H*-dibenzo[*b,d*]pyran-6-ones (DBP) **176** (Scheme 3.9).

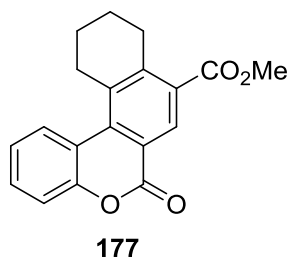


Scheme 3.9 Proposed synthesis of (1,6)pyrenophane **174**.

3.5 Experimental Procedures and Characterization Data

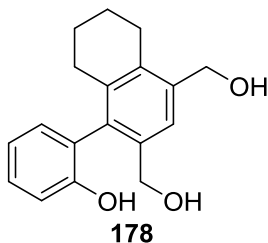
General: Reactions were performed using anhydrous solvents under a balloon containing N₂ unless otherwise indicated. All reactions were performed with oven-dried (120 °C) glassware. THF was distilled immediately prior to use from sodium/benzophenone under N₂ and DMF was vacuum distilled over CaH during workups. Solvents were removed under reduced pressure using a rotary evaporator. Chromatographic separations were performed using Silicycle silica gel 60, particle size 40-63 μ m, unless otherwise mentioned. Thin-layer chromatography (tlc) was performed using commercially precoated plastic-backed POLYGRAM SIL G/UV254 silica gel plates, layer thickness 200 μ m. Compounds on tlc plates were visualized using a UV lamp (254 and 365 nm). Melting points were obtained using an Optimelt automated melting point system and are uncorrected. ¹H and ¹³C NMR spectra were obtained from CDCl₃ or DMSO-d₆ solutions using a Bruker AVANCE (300 MHz) instrument. Chemical shifts: TMS (δ_{H} = 0.00 ppm) and CDCl₃ (δ_{C} = 77.23 ppm), respectively. Low-resolution and high-resolution mass spectrometric data were obtained using an Agilent 1100 series LC/MSD instrument and a Waters Micromass GCT Premier instrument, respectively.

Dibenzopyranone (**177**)



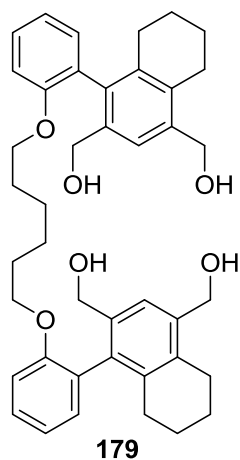
To a solution of dihydrodibenzopyranone **176**¹⁶ (1.00 g, 3.00 mmol) in (10 mL) of reagent grade benzene (10 mL) was added recrystallized DDQ (0.95 g, 4.2 mmol) and the resulting mixture was stirred at room temperature for 30 min. The mixture was then heated at 80 °C overnight (16-18 h). The mixture was gravity filtered and the filter cake was washed with chloroform (30 mL). The filtrate was concentrated under reduced pressure and the residue was subjected to column chromatography (3.5 × 23 cm) to afford compound **177** in 93% yield (1.42 g, 4.61 mmol) as a brown solid. R_f (30% ethyl acetate/hexanes) = 0.51; mp = 157-159 °C; ^1H NMR (300 MHz, CDCl_3) δ = 8.76 (s, 1H), 8.30 (dd, J = 8.3, 1.1 Hz, 1H), 7.51 (ddd, J = 8.3, 7.0, 1.3 Hz, 1H), 7.40 (dd, J = 8.2, 1.5 Hz, 1H), 7.33 (ddd, J = 8.6, 7.1, 1.6 Hz, 1H), 3.94 (s, 3H), 3.34-3.29 (m, 4H), 1.96-1.88 (m, 2H), 1.86-1.78 (m, 2H); ^{13}C NMR: (75 MHz, CDCl_3) δ = 166.05, 161.02, 155.33, 151.94, 141.81, 134.47, 132.06, 130.76, 126.89, 126.75, 126.65, 124.37, 120.40, 118.85, 117.94, 52.15, 35.33, 33.62, 25.00; MS (APCI-(+), CH_2Cl_2): m/z (%) 309 (100, $[\text{M}+1]^+$), 310 (22); HRMS (TOF-MS-APCI): Calc. for $\text{C}_{19}\text{H}_{16}\text{O}_4$: 308.1049, Found: 308.1051.

1,2,3,4-Tetrahydro-6,8-bis(hydroxymethyl)-5-(2-hydroxyphenyl)naphthalene (178)



To a 0 °C slurry of LiAlH₄ (0.83 g, 22 mmol) in THF was added compound **177** (1.70 g, 5.50 mmol) in several portions and the resulting mixture was heated to 70 °C for 5 h. After cooling to 0 °C, water (20 mL) was added carefully over a period of 20 min. The reaction mixture was diluted with aqueous 1.0 M HCl solution (100 mL) and extracted with CHCl₃ (3 × 200 mL). The combined organic layers were dried over Na₂SO₄, gravity filtered and the solvent was removed under reduced pressure. The residue was triturated with ether (2 × 15 mL) to afford compound **172** (1.42 g, 5.21 mmol, 96%) as a colorless solid. *R_f* = 0.60 (ethyl acetate); mp 148-150 °C; ¹H NMR δ = 7.40 (s 1H), 7.14 (ddd, *J* = 8.5, 6.1, 3.0 Hz, 1H), 6.89 (d, *J*=8.0 Hz, 1H), 6.84-6.80 (m, 2H), 4.49 (t, *J* = 5.3 Hz, 1H), 4.75 (brs, 1H), 4.49 (d, *J* = 5.0 Hz, 2H), 2.67 (brt, *J* = 6.1 Hz, 2H), 2.23 (brt, *J* = 6.2 Hz, 2H) 1.76-1.51 (m, 4H); ¹³C NMR (DMSO-*d*₆, 300 MHz) δ = 154.16, 138.16, 136.70, 134.67, 134.16, 131.82, 130.50, 128.13, 126.07, 122.25, 119.07, 115.45, 61.22, 61.01, 27.62, 25.01, 22.56, 22.46; MS (APCI(-), CH₂Cl₂): *m/z* (%) 283 (100, [M-1]⁻) 284 (13); HRMS (TOF-MS-APCI): Calc. for C₁₈H₂₀O₃: 284.1412, Found: 284.1418.

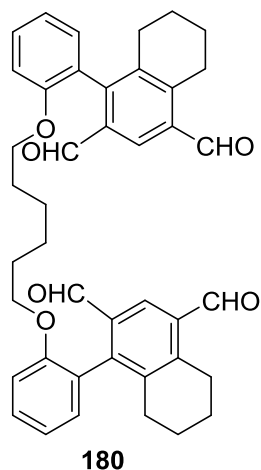
1,6-Bis(2-(1,2,3,4-tetrahydro-6,8-bis(hydroxymethyl)naphth-5-yl)phenoxy)hexane
(179)



To a suspension of triol (**178**) (0.80 g, 3.0 mmol) and K_2CO_3 (1.24 g, 8.50 mmol) in DMF (15 mL) was added 1,6-dibromohexane (0.39 g, 1.6 mmol). The resulting mixture was stirred vigorously at 90 °C for 16 h and then cooled to room temperature. Water (30 mL) was added and the resulting mixture was extracted with ethyl acetate (3×30 mL). The combined organic layers were washed with water (50 mL), dried over $NaSO_4$, gravity filtered and the solvent was removed under reduced pressure. The residue was subjected to column chromatography (5% MeOH / $CHCl_3$) to obtain tetraol **179** 83% (0.79 g, 1.2 mmol) as a colorless solid. R_f = 0.40; mp = 131-133 °C; 1H NMR (300 MHz, $DMSO-d_6$) δ = 7.41 (s, 2H), 7.32-7.27 (m, 2H), 7.03-6.89 (m, 6H), 4.98 (t, J = 5.0 Hz, 2H), 4.76 (t, J = 5.1 Hz, 2H), 4.48 (d, J = 5.0 Hz, 2H), 4.03-4.01 (m, 4H), 3.87-3.77 (m, 4H), 2.62-2.59

(m, 4H), 2.17-2.15 (m, 4H), 1.66-1.60 (m, 4H), 1.54-1.46 (m, 4H), 1.40-1.38 (m, 4H), 1.16-1.07 (m, 4H); ^{13}C NMR: (75 MHz, DMSO- d_6) δ = 155.53, 138.41, 138.21, 136.21, 136.17, 136.10, 135.66, 135.52, 134.13, 134.02, 130.83, 128.91, 128.79, 126.54, 124.36, 124.28, 121.16, 121.12, 112.92, 68.50, 68.40, 63.72, 63.57, 62.58, 62.56, 36.35, 31.28, 28.65, 28.46, 28.33, 25.67, 25.21, 25.10, 22.83, 22.80 ; MS (APCI-(+), CH_2Cl_2): m/z (%) 649 (25, $[\text{M}-1]^+$), 650 (100); HRMS (TOF-MS-APCI): Calc. for $\text{C}_{42}\text{H}_{50}\text{O}_6$: 650.3610, Found: 650.3612.

1,6-Bis (2-(6, 8-diformyl-2, 3-dihydro-1H-hexen-4-yl)phenoxy)hexane (180)



To a solution of tetraol (**179**) (1.00 g, 2.00 mmol) in CH_2Cl_2 (45 mL) was added Celite (3.00 g) in one portion. To this suspension was added PCC (4.05 g, 18.8 mmol) in several portions and the resulting mixture was stirred at room temperature for 3 h. The reaction mixture was vacuum filtered through a plug of Celite and the cake was washed thoroughly with CHCl_3 (3×50 mL). The filtrate was removed under reduced pressure and the residue was subjected to column chromatography (30% ethyl acetate / hexanes) to afford tetraaldehyde (**180**) 62% (0.65 g, 0.91 mmol) as a colorless solid. $R_f = 0.30$ (30% ethyl acetate / hexanes); mp = 168-171 °C; ^1H NMR (300 MHz, CDCl_3) indicates the presence of two diastereomers in a 2:1 ratio. The differences were seen only in the aromatic region. Major diastereomer: $\delta = 10.27$ (s, 2H), 9.58 (s, 2H), 8.24 (s, 2H), 7.45-7.42 (m, 2H), 7.08-7.06 (m, 4H), 6.97 (d, $J = 8.3$ Hz, 2H). Minor diastereomer: $\delta = 10.24$

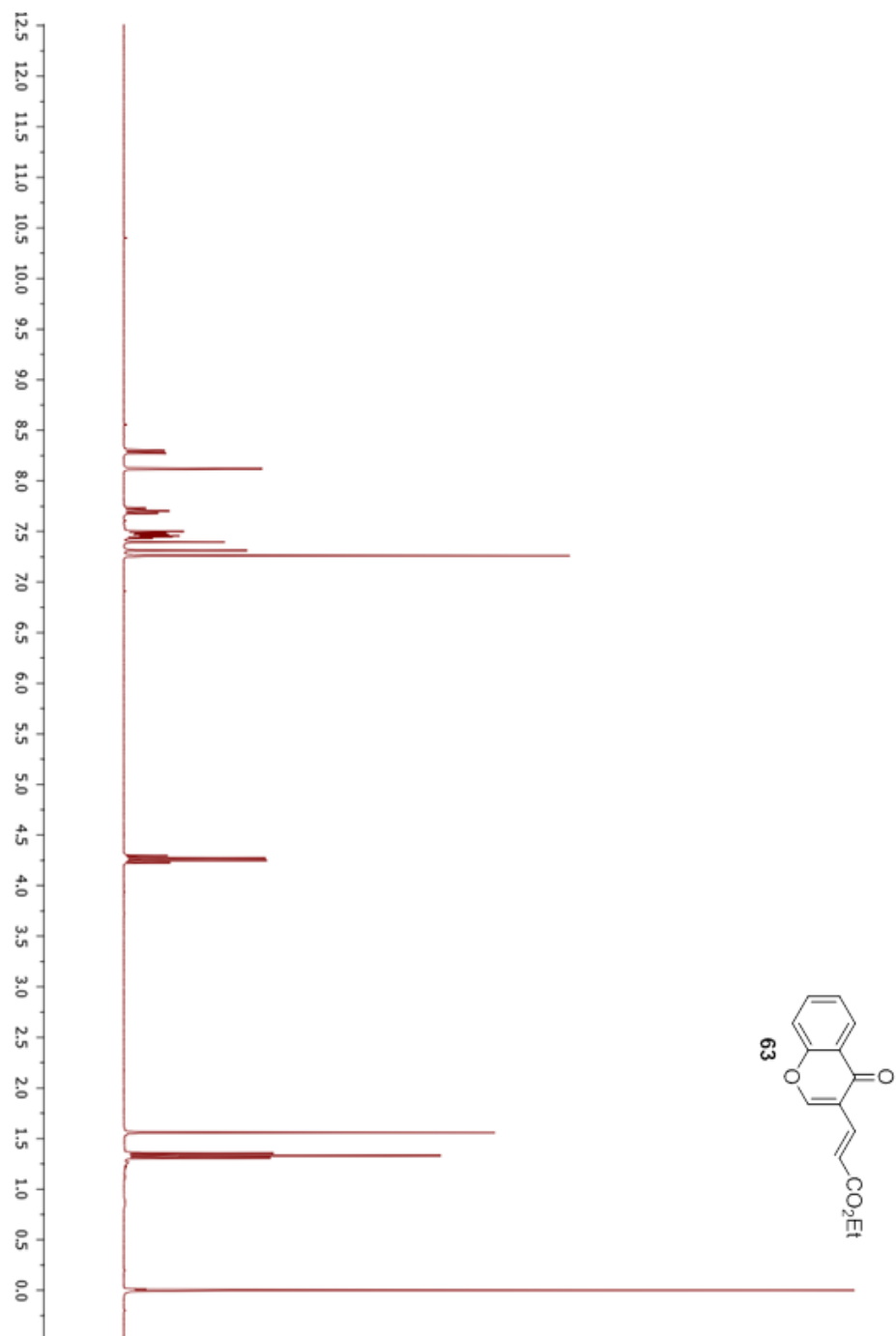
(s, 2H), 9.59 (s, 2H), 8.23 (s, 2H), 7.41-7.39 (m, 2H), 7.06-7.04 (m, 4H), 6.98 (d, $J = 8.2$ Hz, 2H). Remaining signals for the mixture of diastereomers: $\delta = 3.83$ (t, $J = 6.3$ Hz, 4H), 3.32-3.26 (m, 4H), 2.48-2.28 (m, 4H), 1.81-1.57 (m, 8H), 1.44-1.40 (m, 4H), 1.05-1.03 (m, 4H) ; ^{13}C NMR: (75 MHz, CDCl_3) $\delta = 192.91, 192.12, 191.91, 155.80, 147.64, 145.57, 138.87, 137.37, 134.57, 133.38, 132.14, 131.06, 130.69, 130.10, 129.93, 129.87, 128.70, 124.57, 123.95, 120.72, 118.29, 111.85, 67.84, 32.90, 29.71, 28.74, 27.84, 25.41, 22.73, 22.05, 21.71$; MS (APCI-+), CH_2Cl_2): m/z (%) 643 (100, $[\text{M}+1]^+$), 644 (41); HRMS (TOF-MS-APCI): Calc. for $\text{C}_{42}\text{H}_{42}\text{O}_6$: 642.2981, Found: 642.2982.

3.6 References

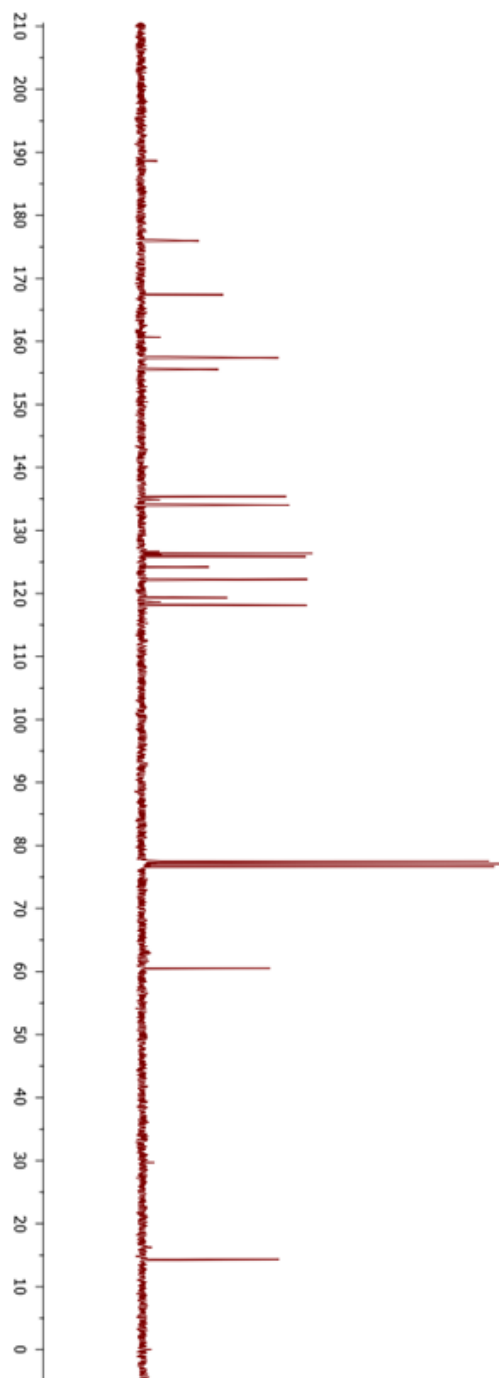
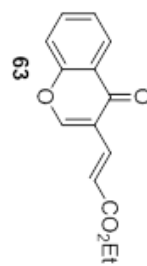
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4.0 Appendix

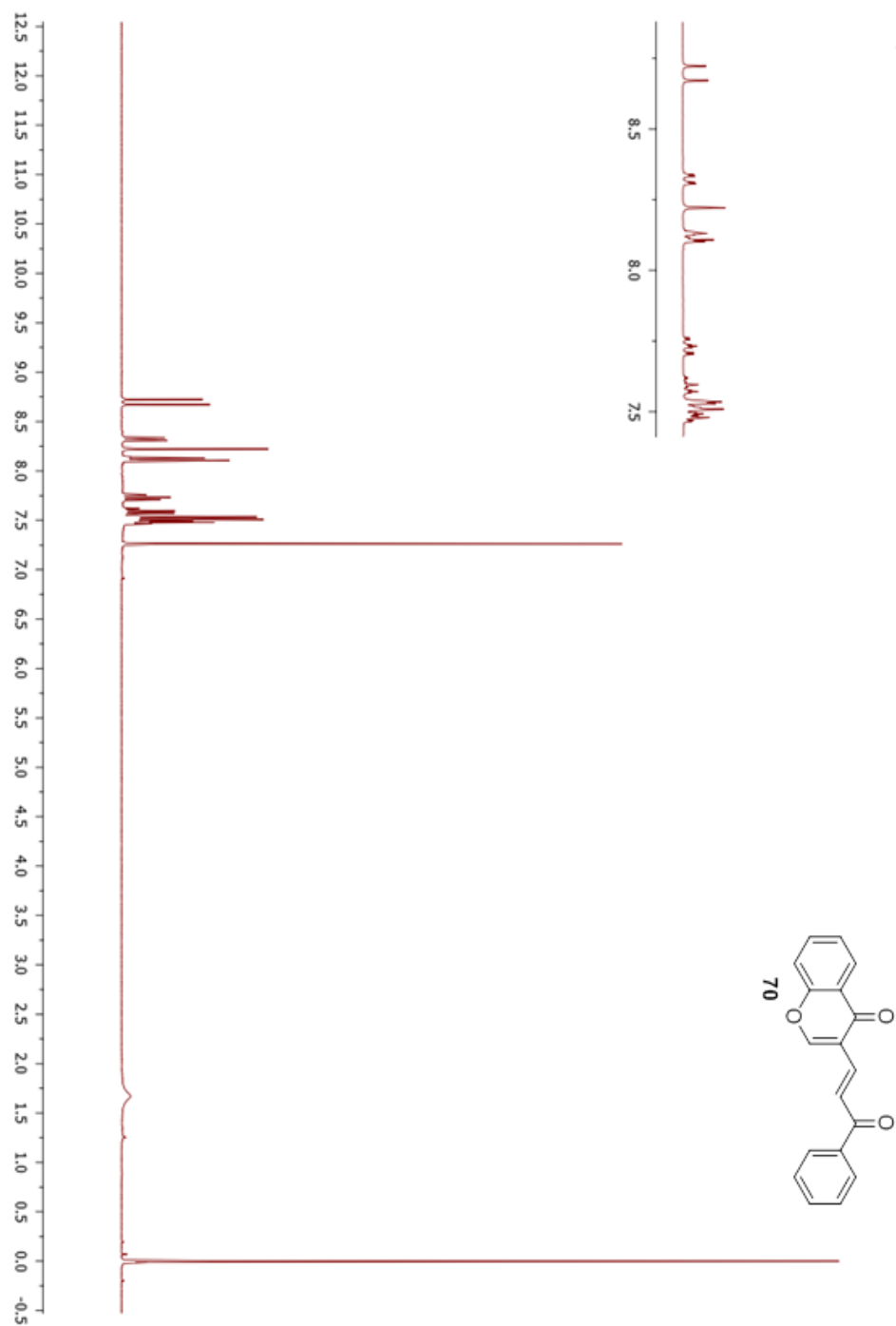
Selected NMR spectra



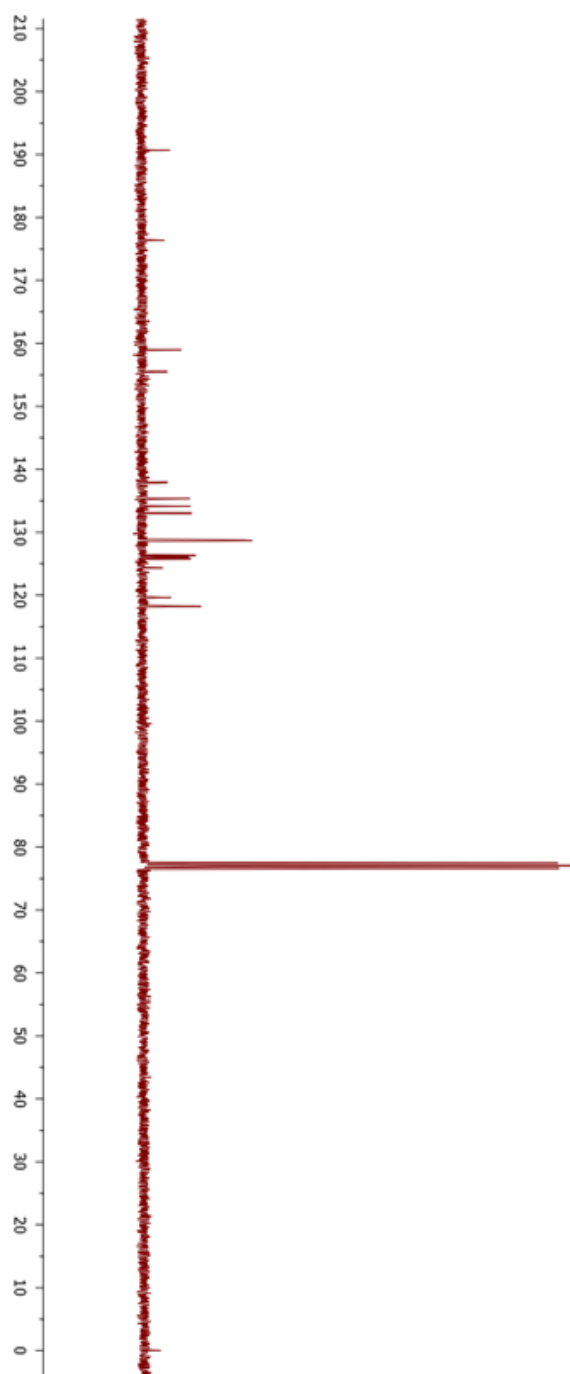
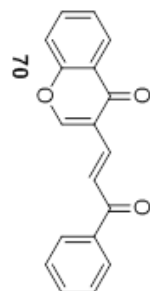
^1H NMR spectrum of **63** in CDCl_3



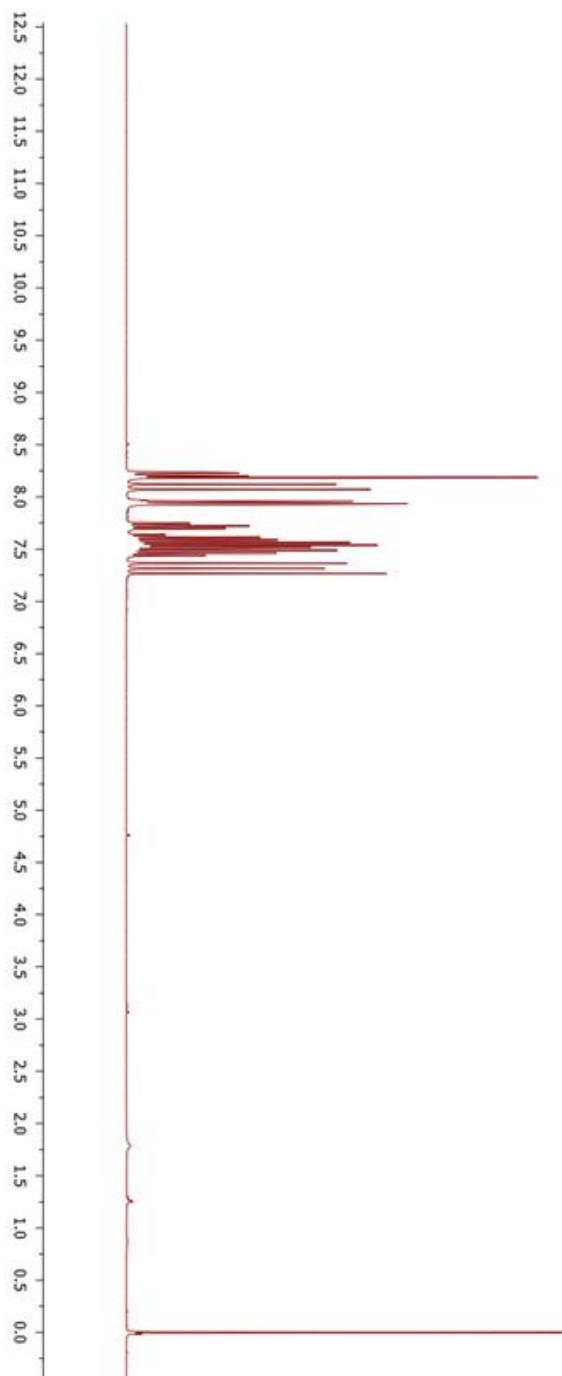
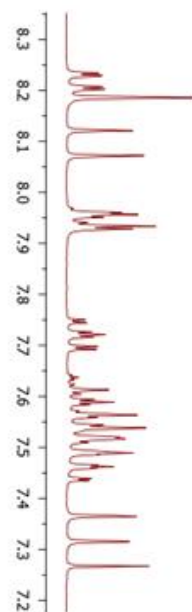
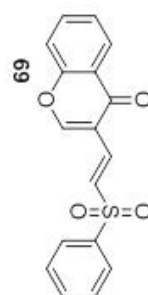
^{13}C NMR spectrum of **63** in CDCl_3



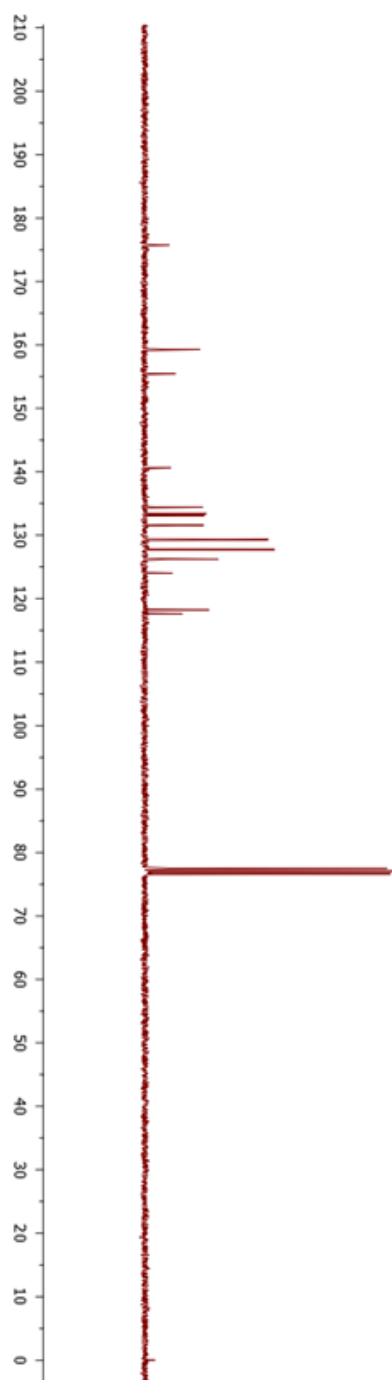
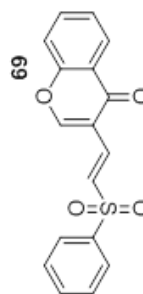
^1H NMR spectrum of **70** in CDCl_3



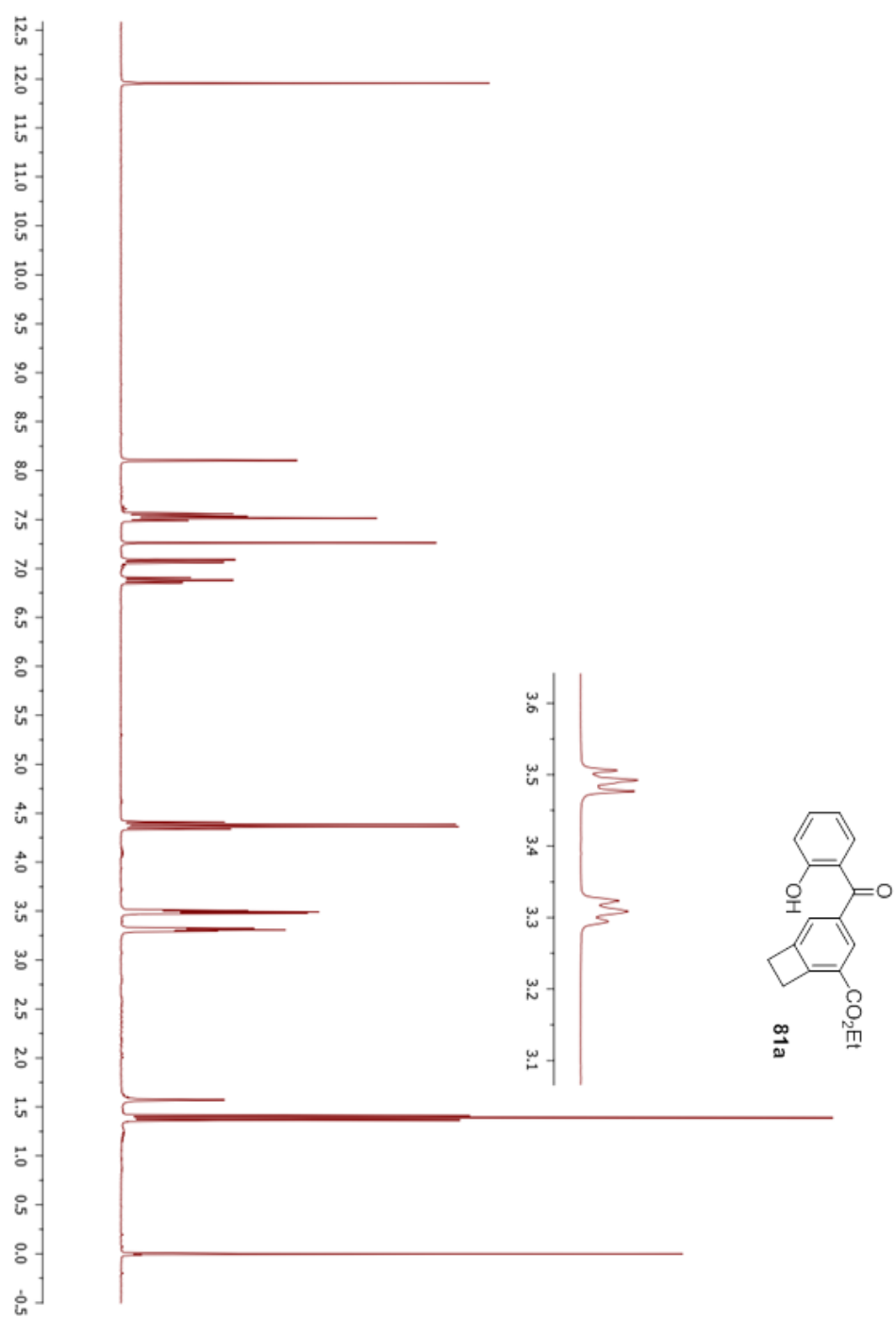
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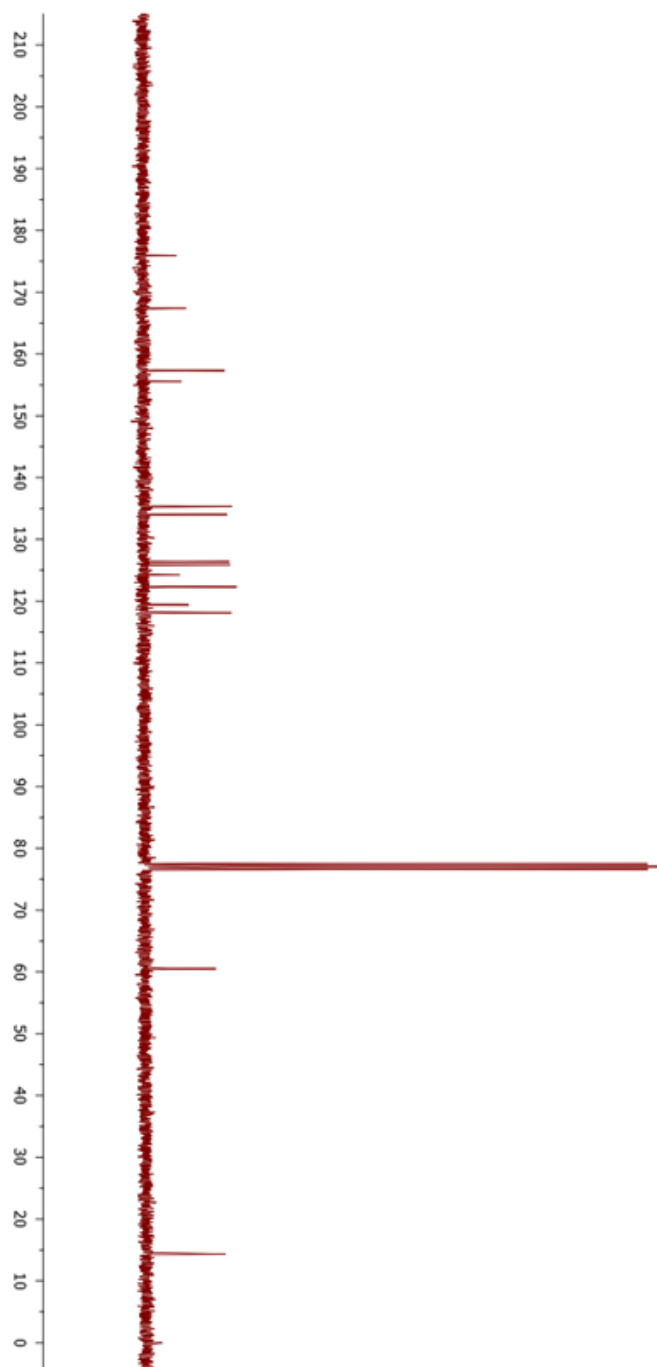
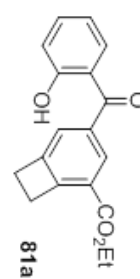
^1H NMR spectrum of **69** in CDCl_3



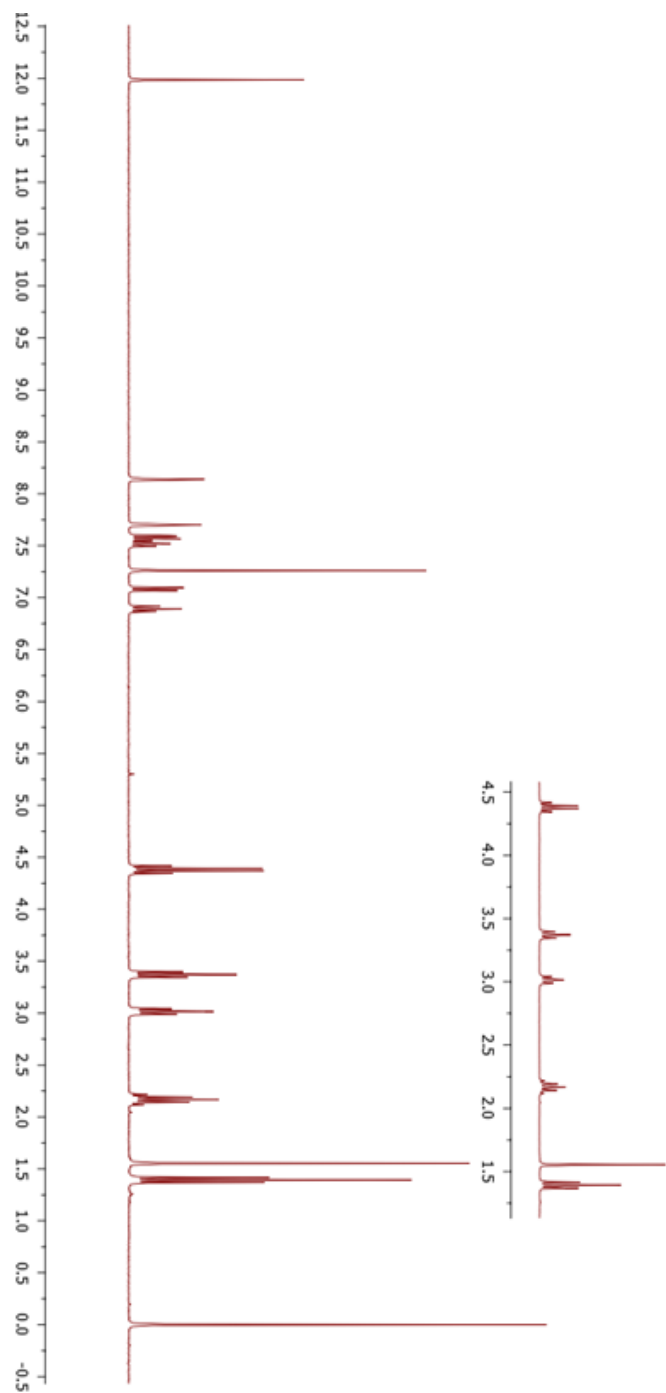
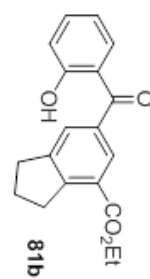
^{13}C NMR spectrum of **69** in CDCl_3



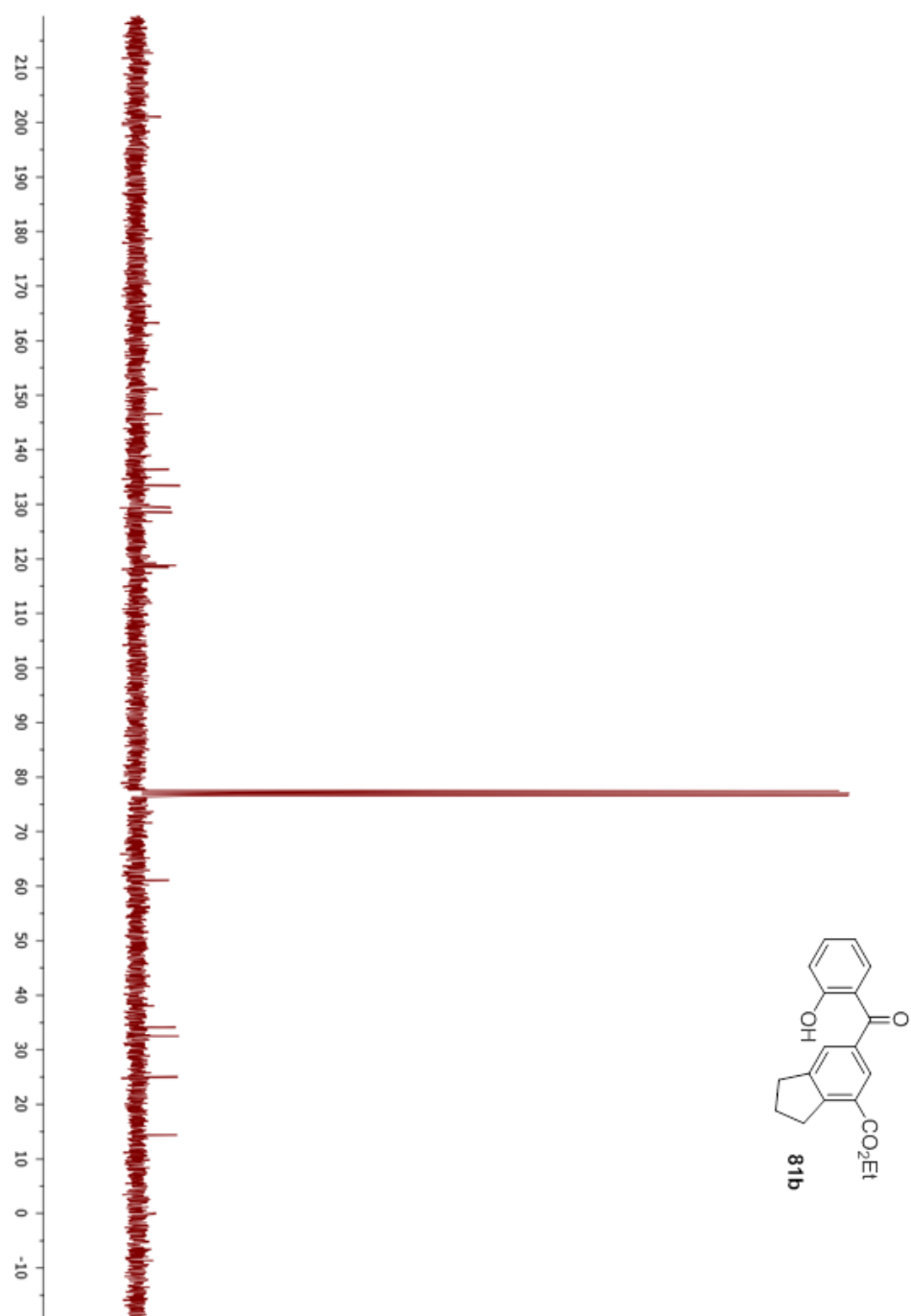
¹H NMR spectrum of **81a** in CDCl₃



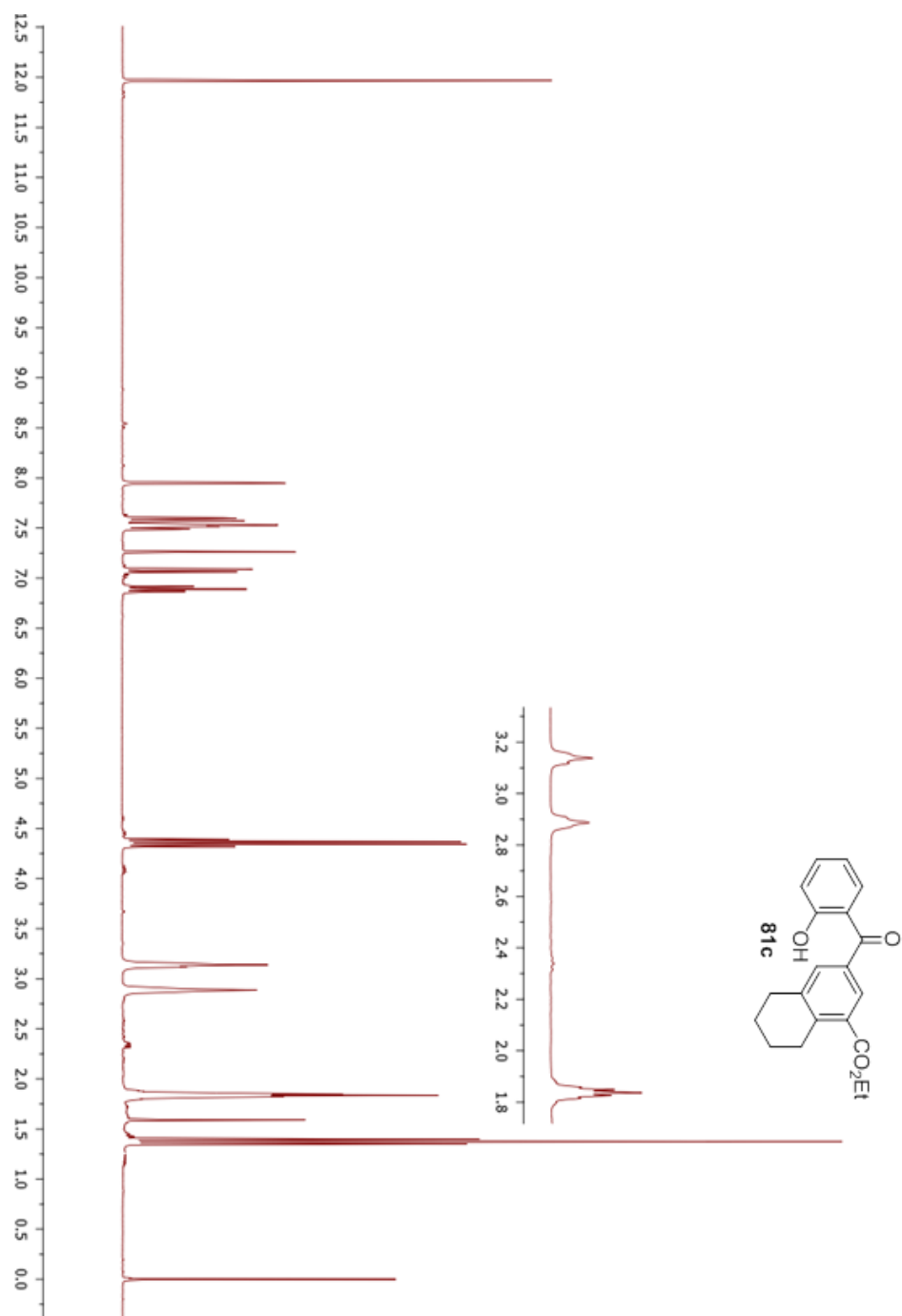
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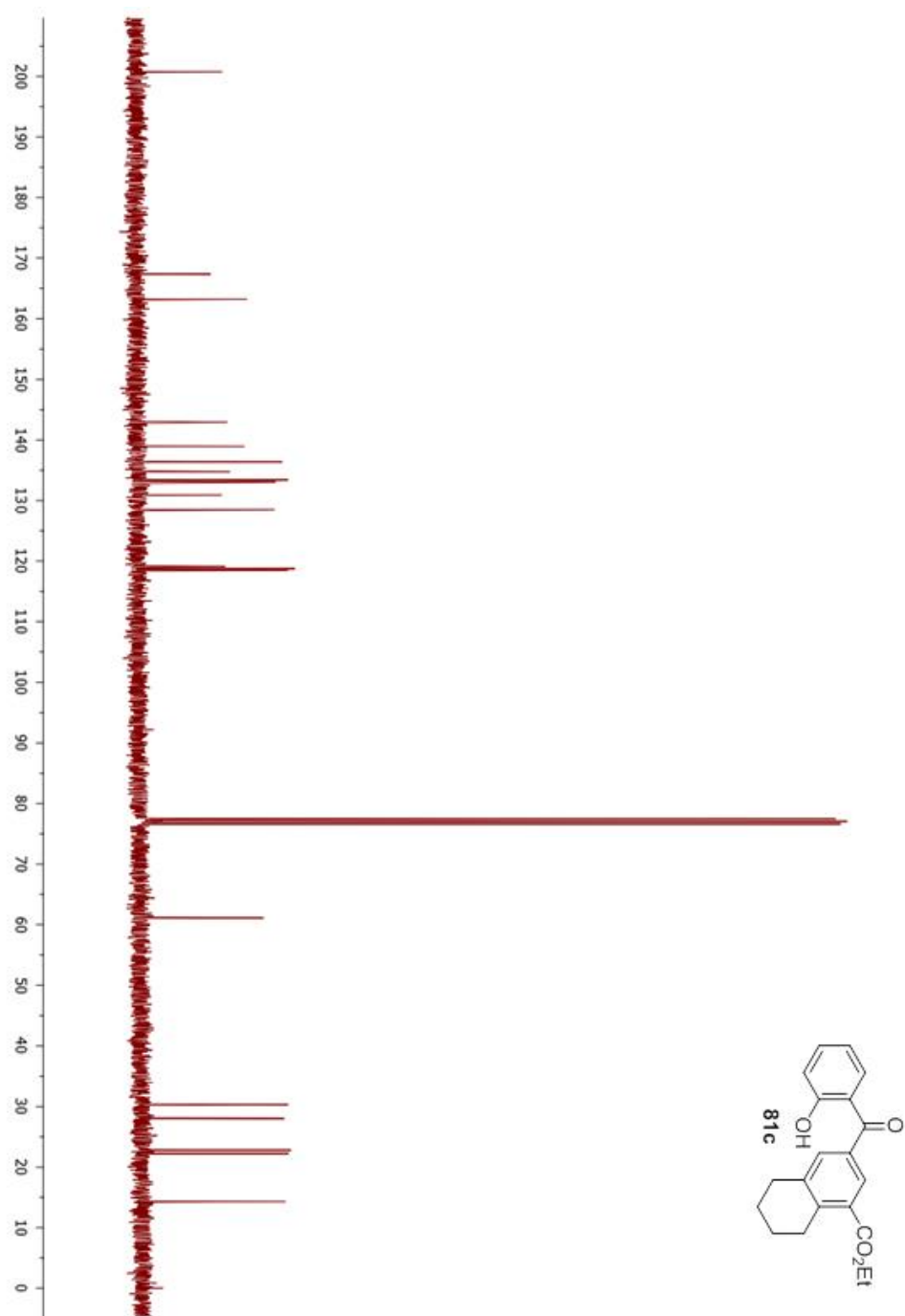
^1H NMR spectrum of **81b** in CDCl_3



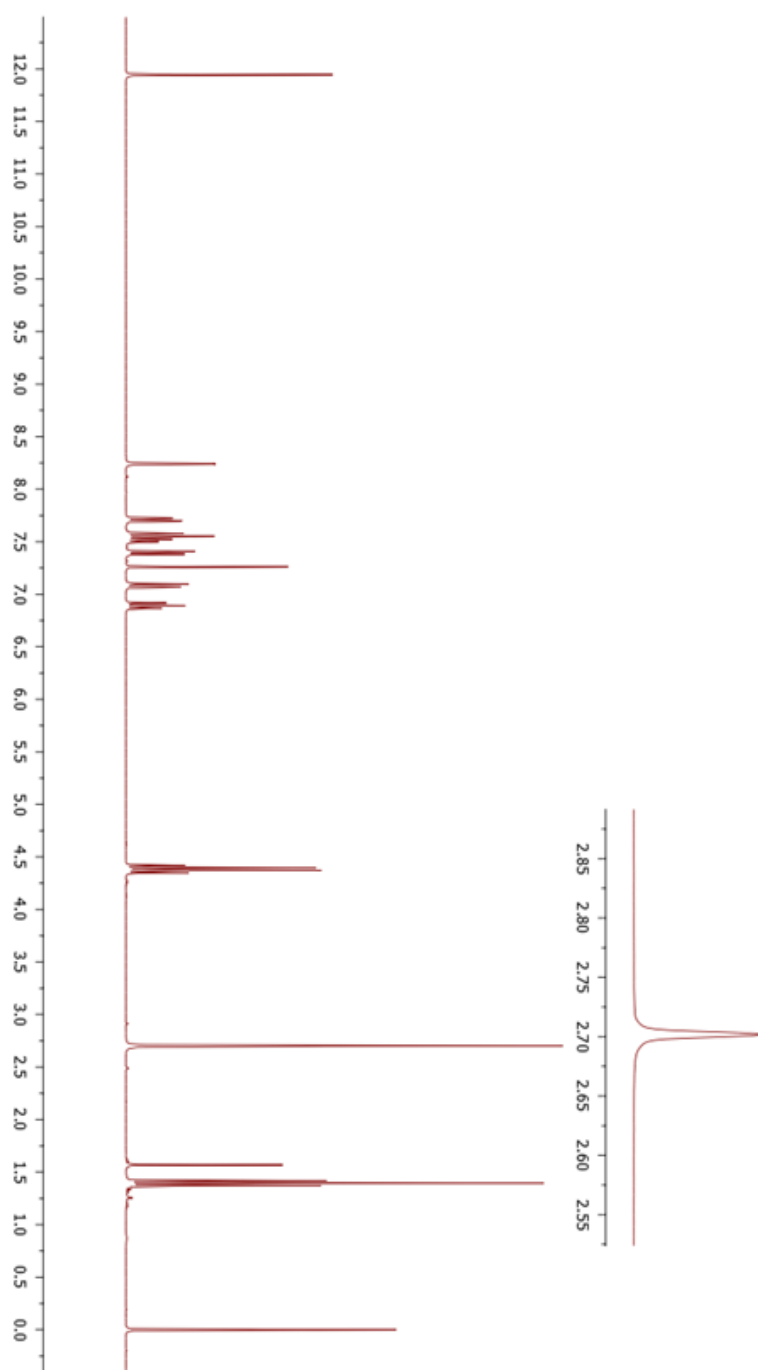
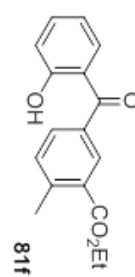
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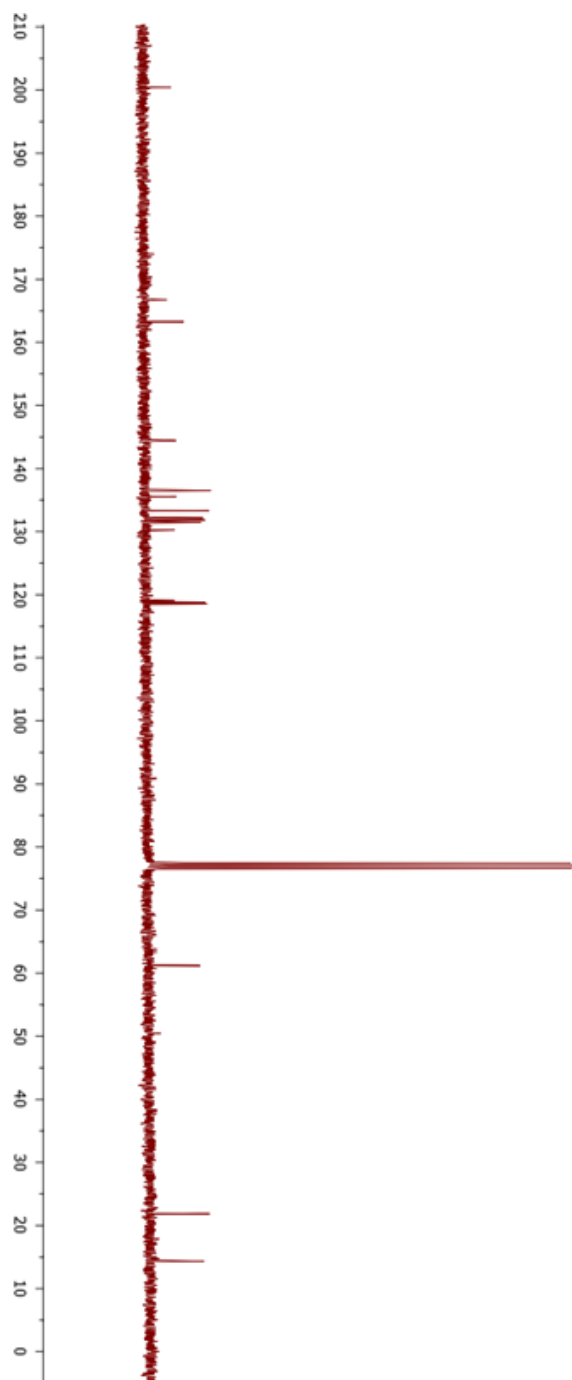
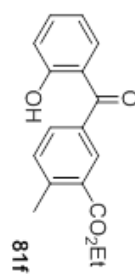
^1H NMR spectrum of **81c** in CDCl_3



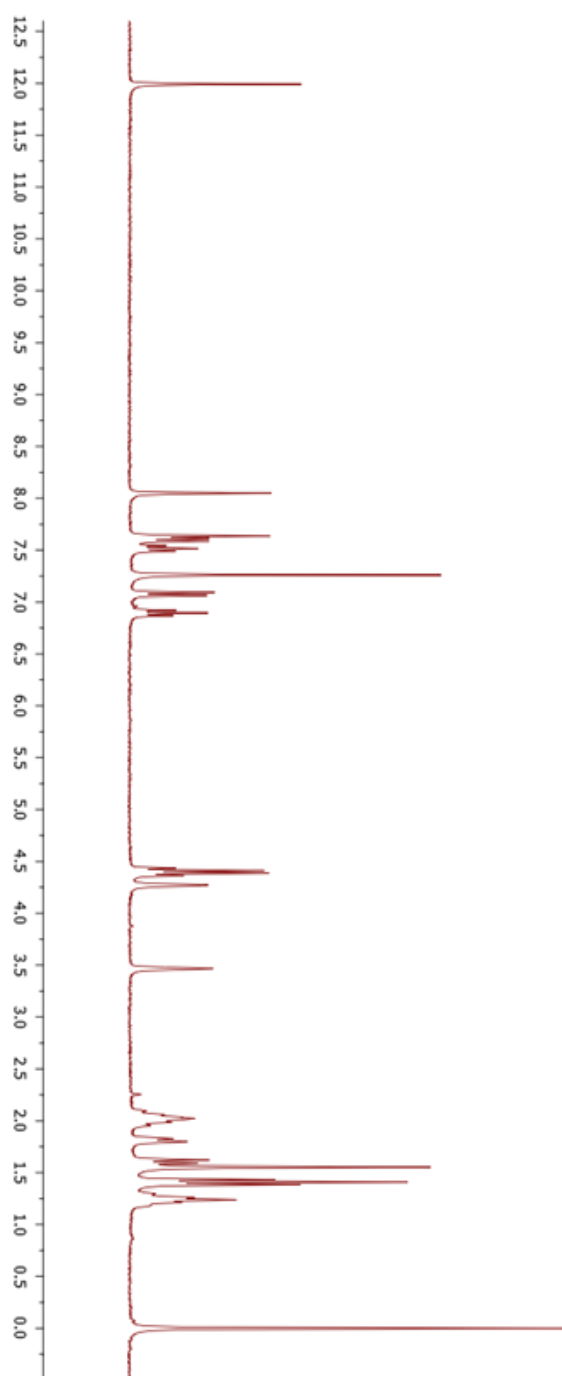
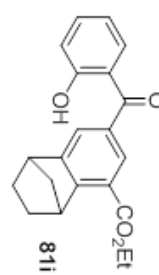
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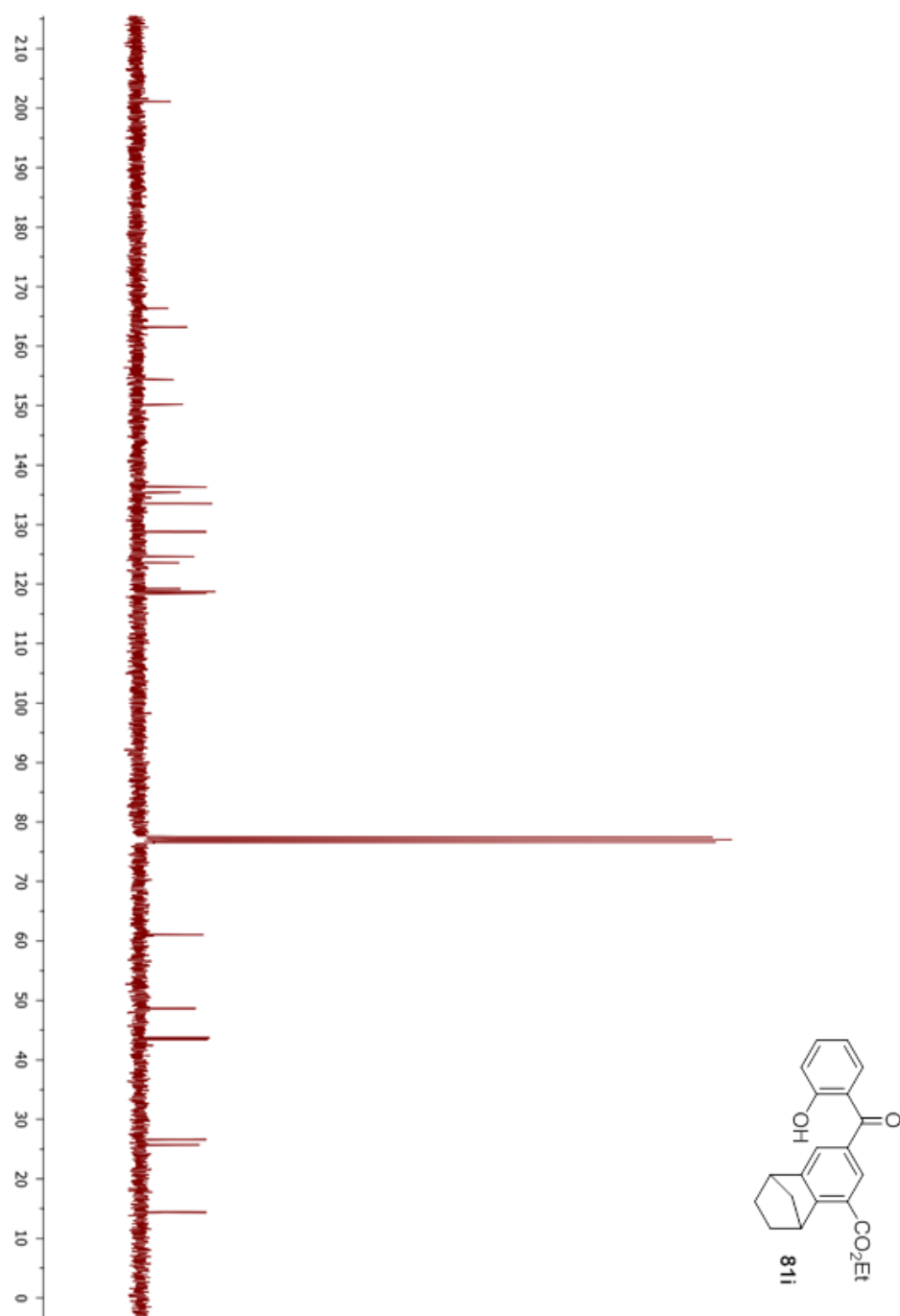
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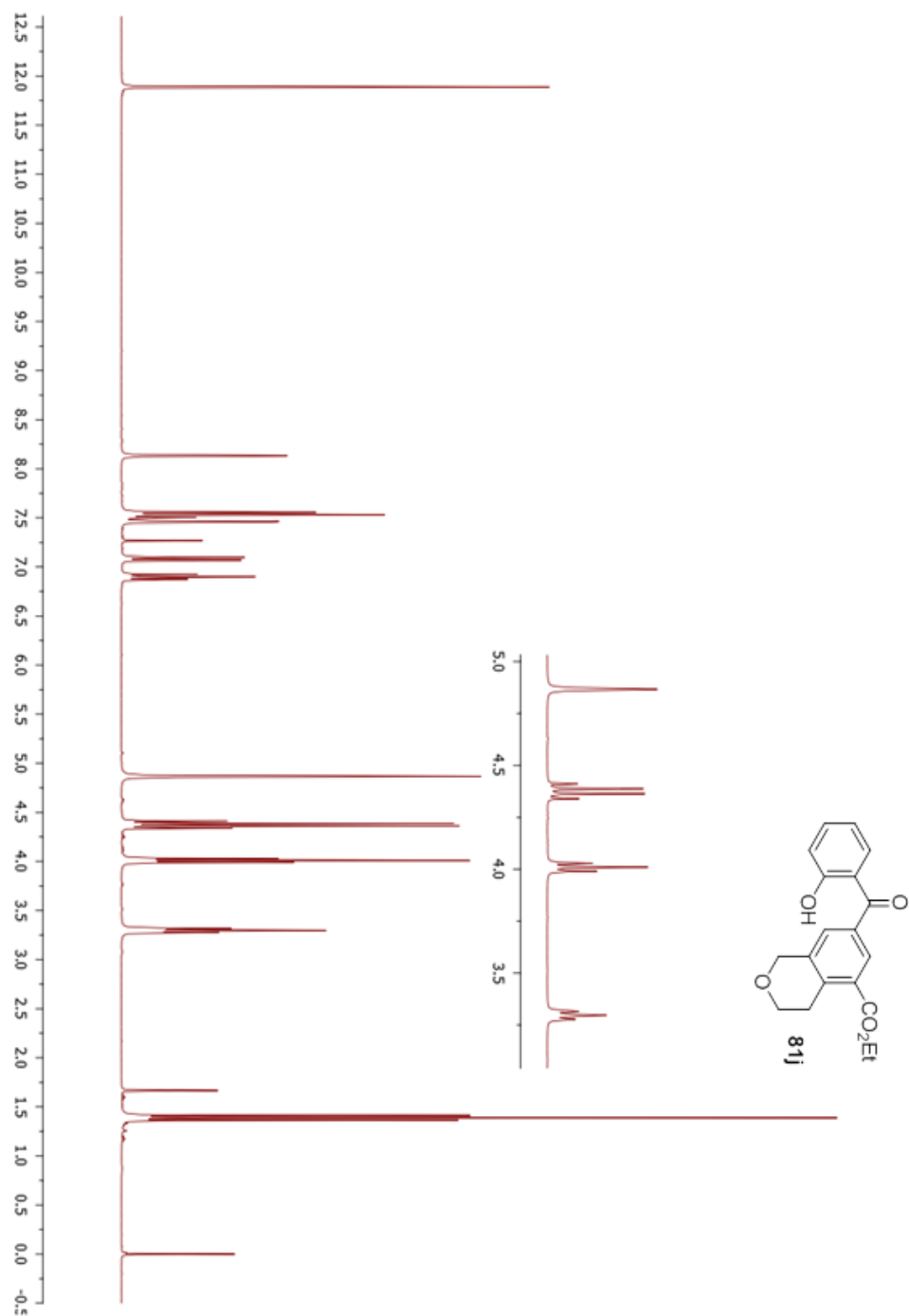
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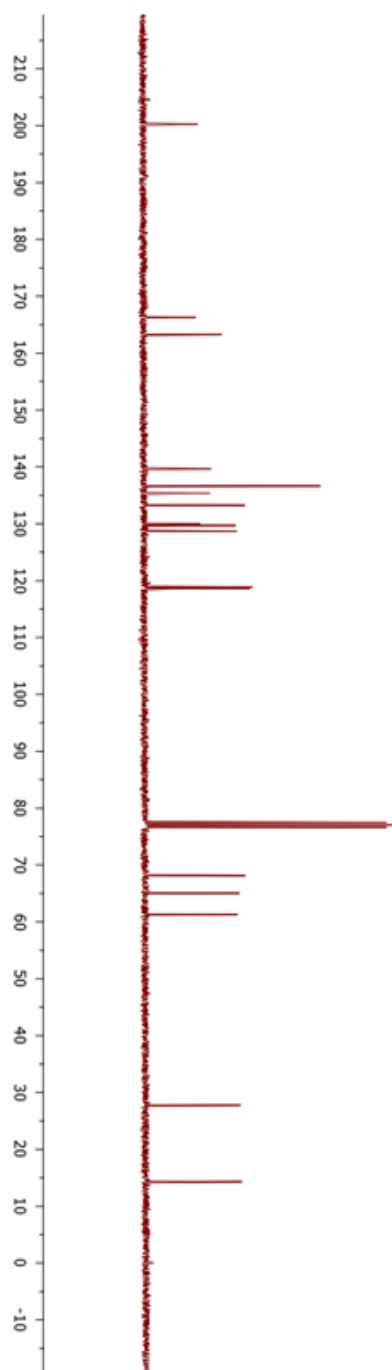
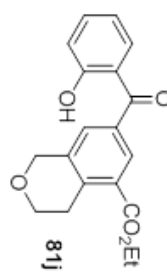
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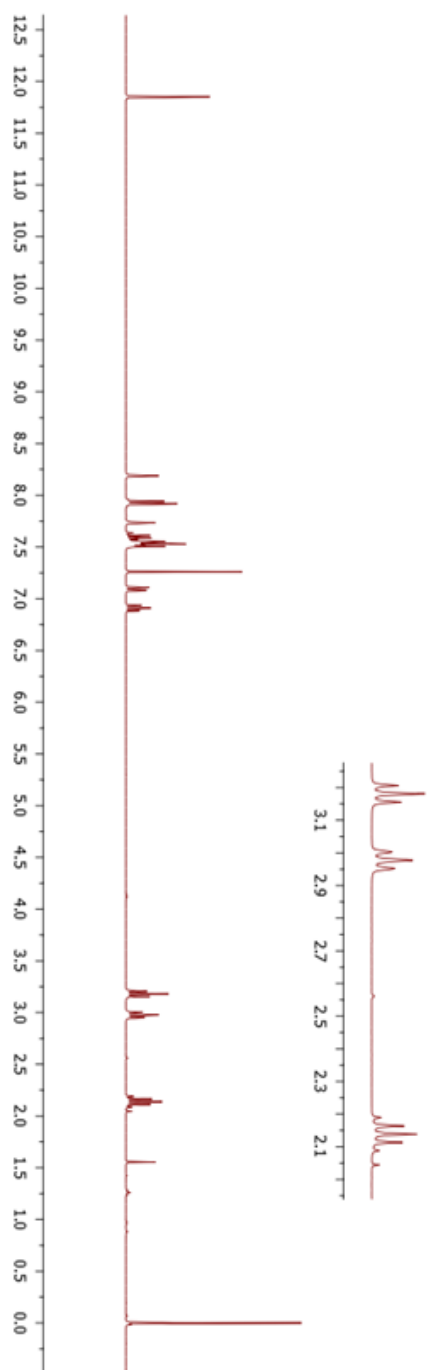
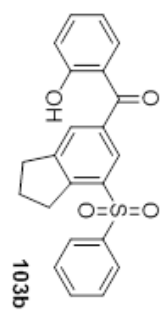
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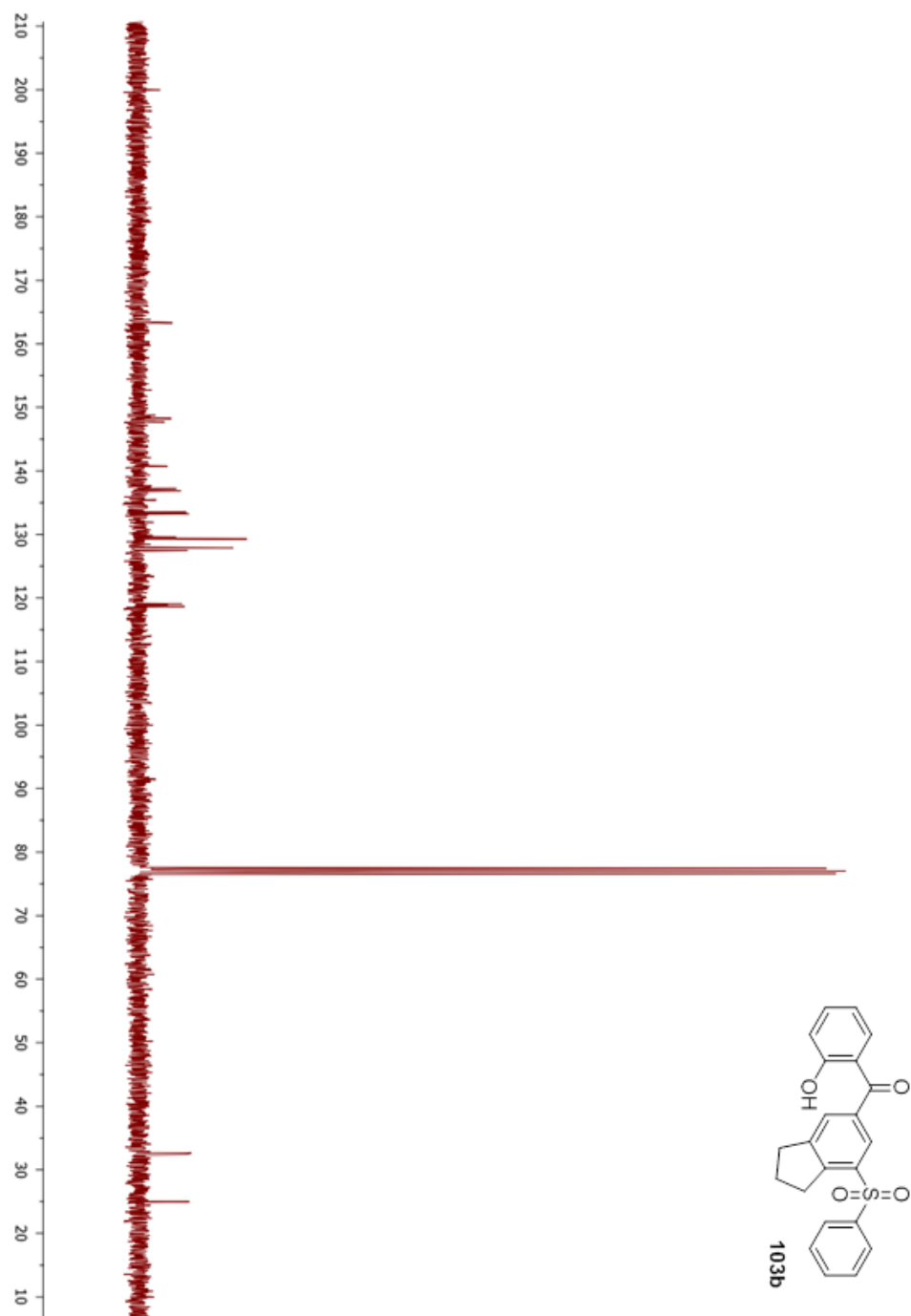
¹H NMR spectrum of **81j** in CDCl₃



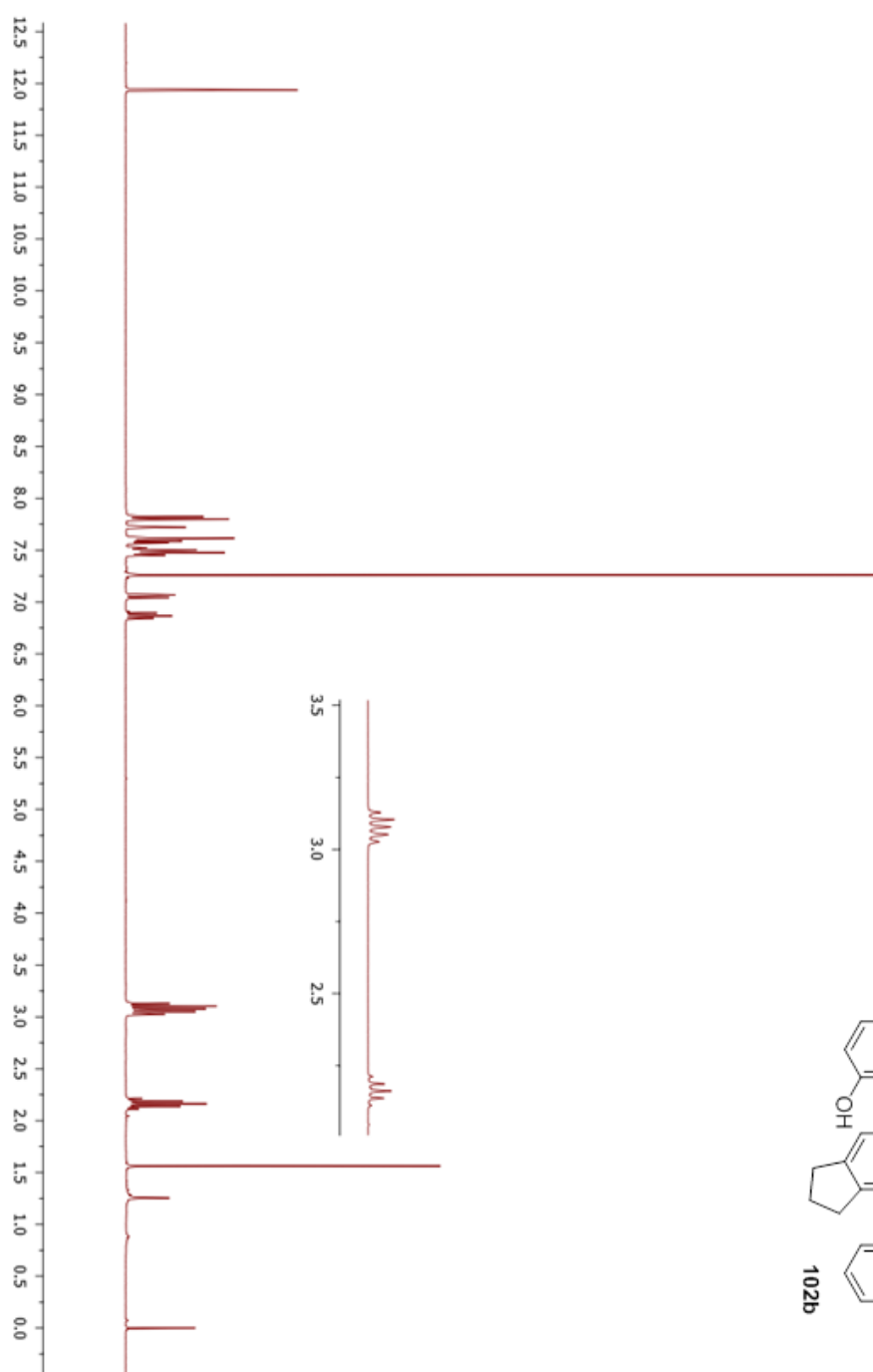
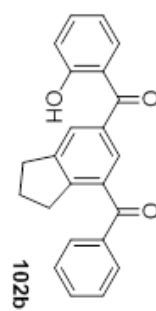
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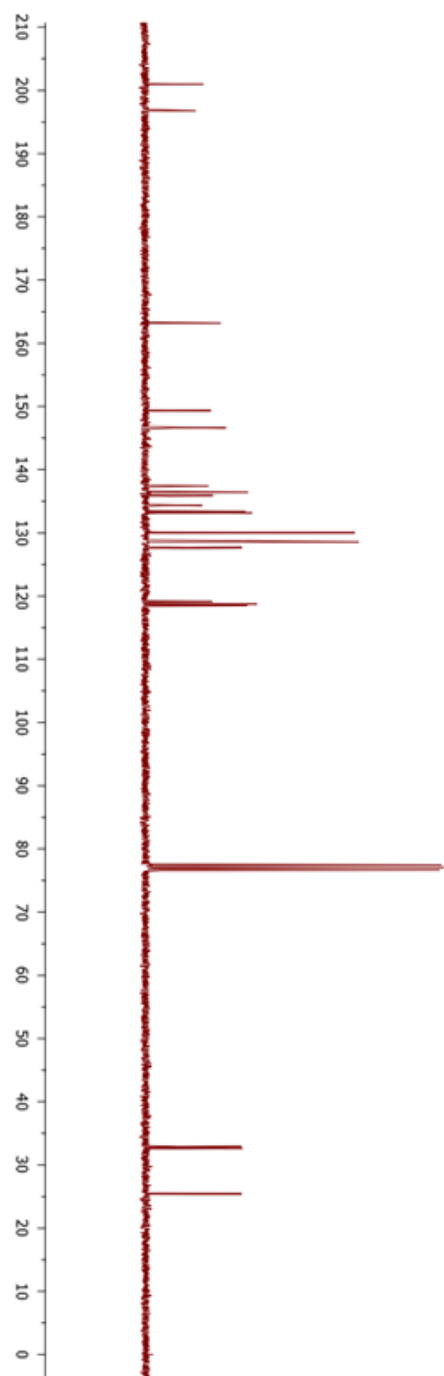
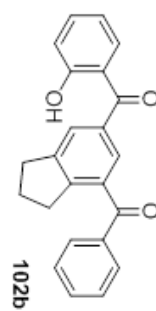
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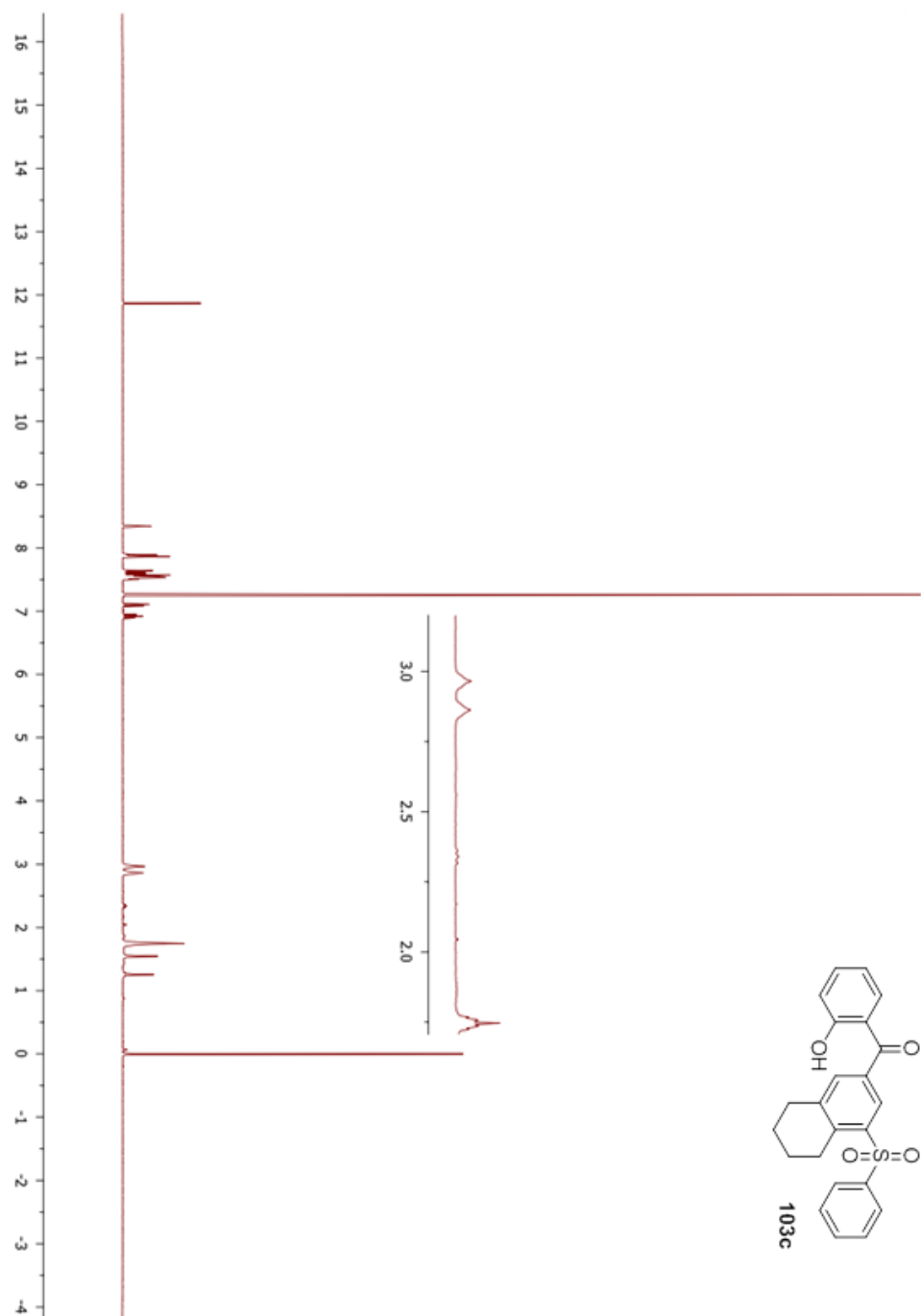
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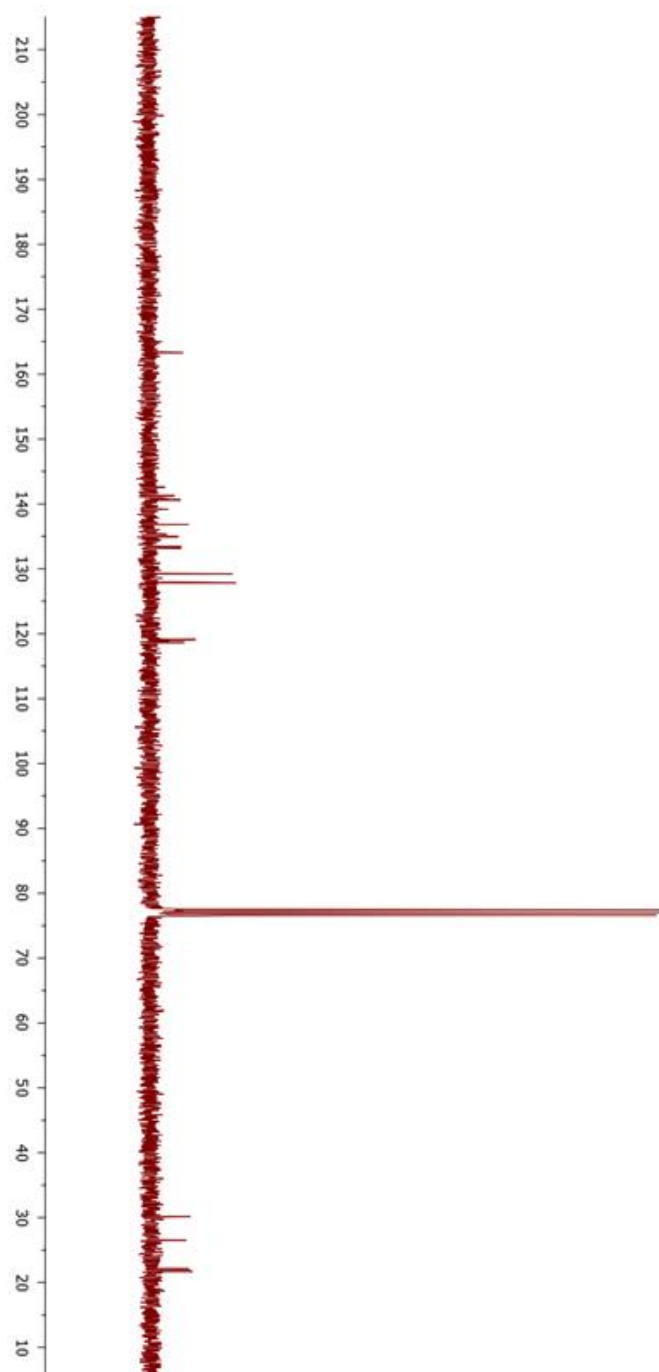
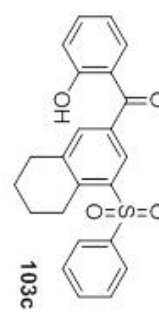
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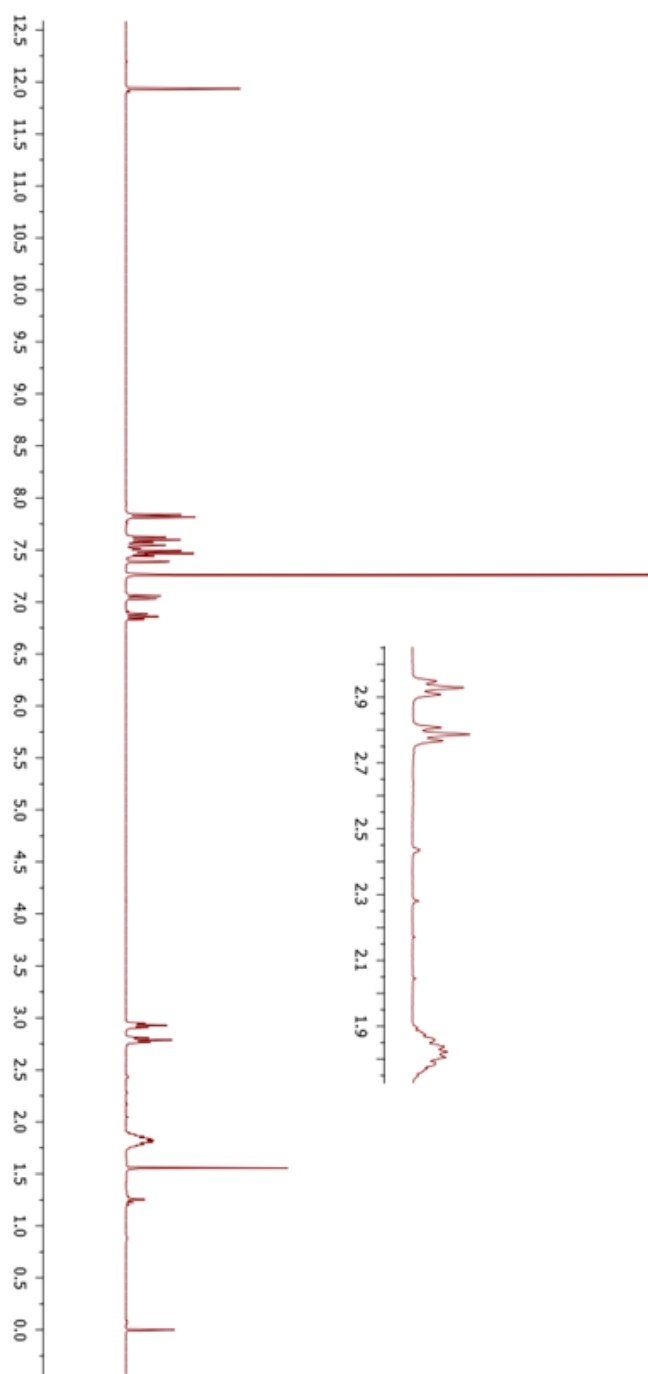
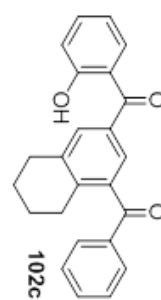
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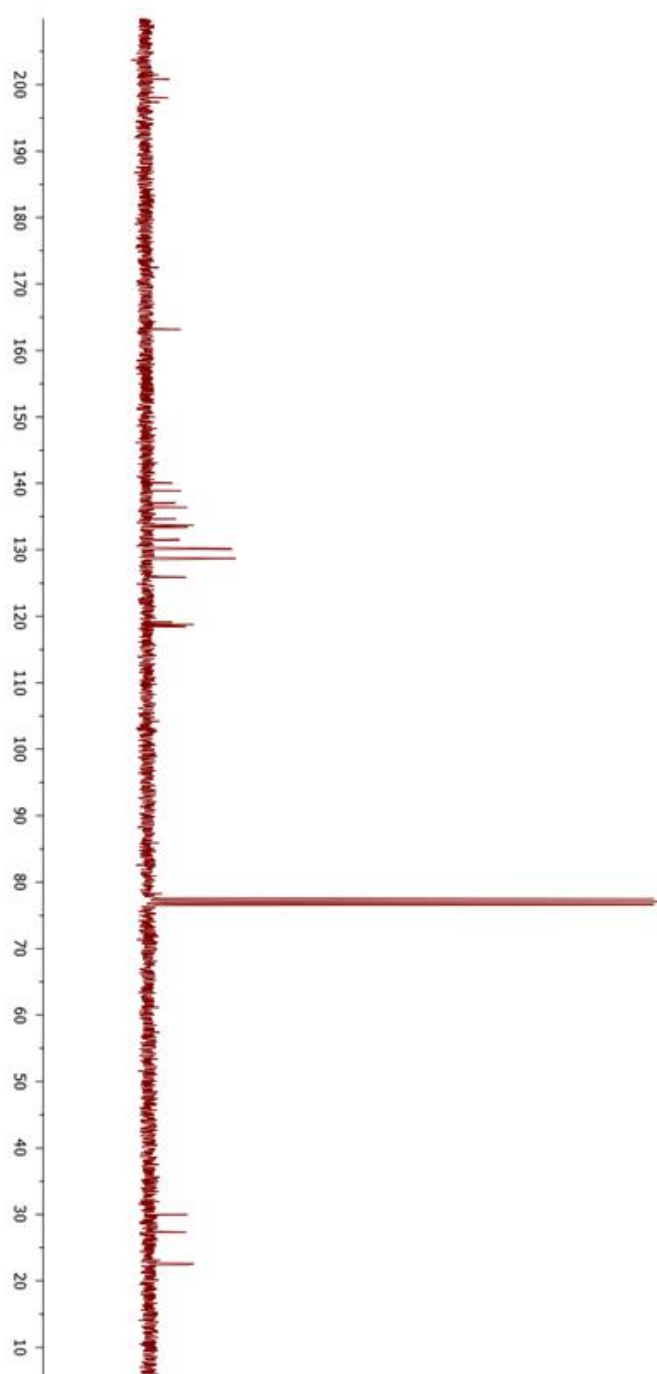
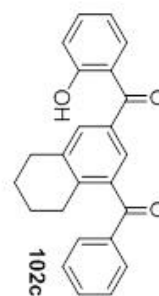
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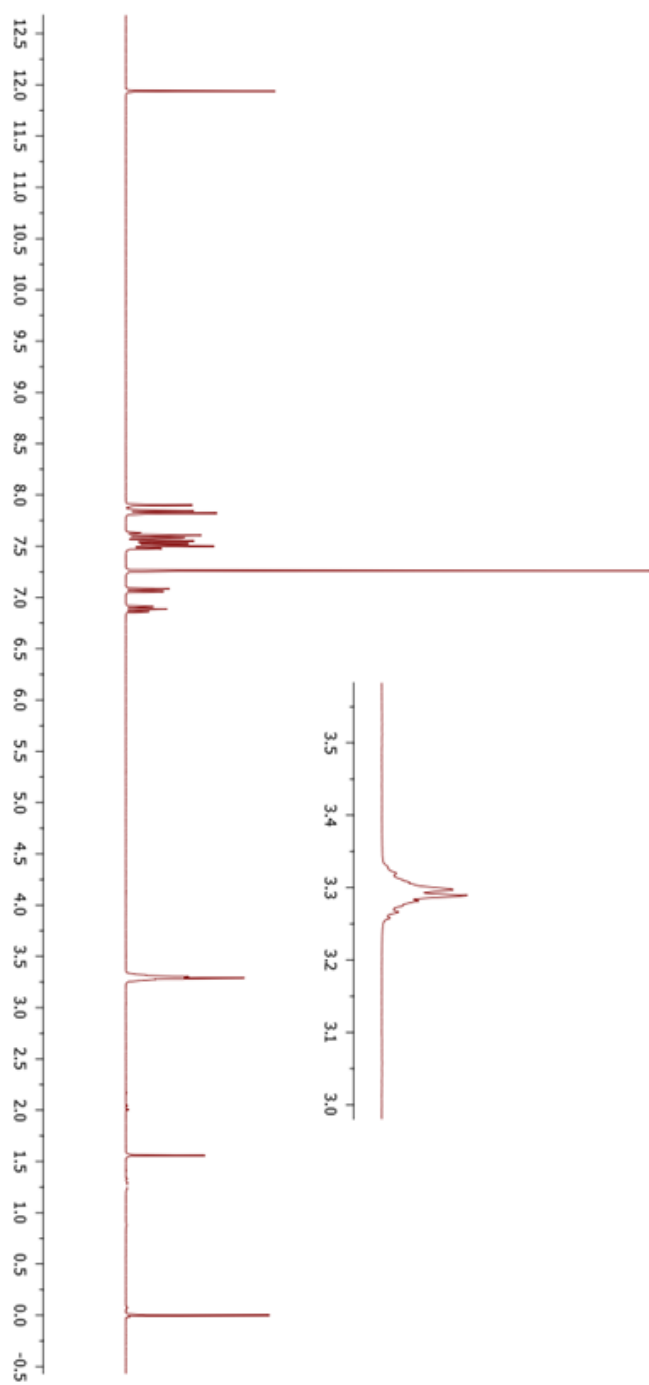
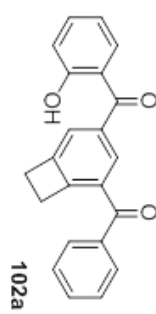
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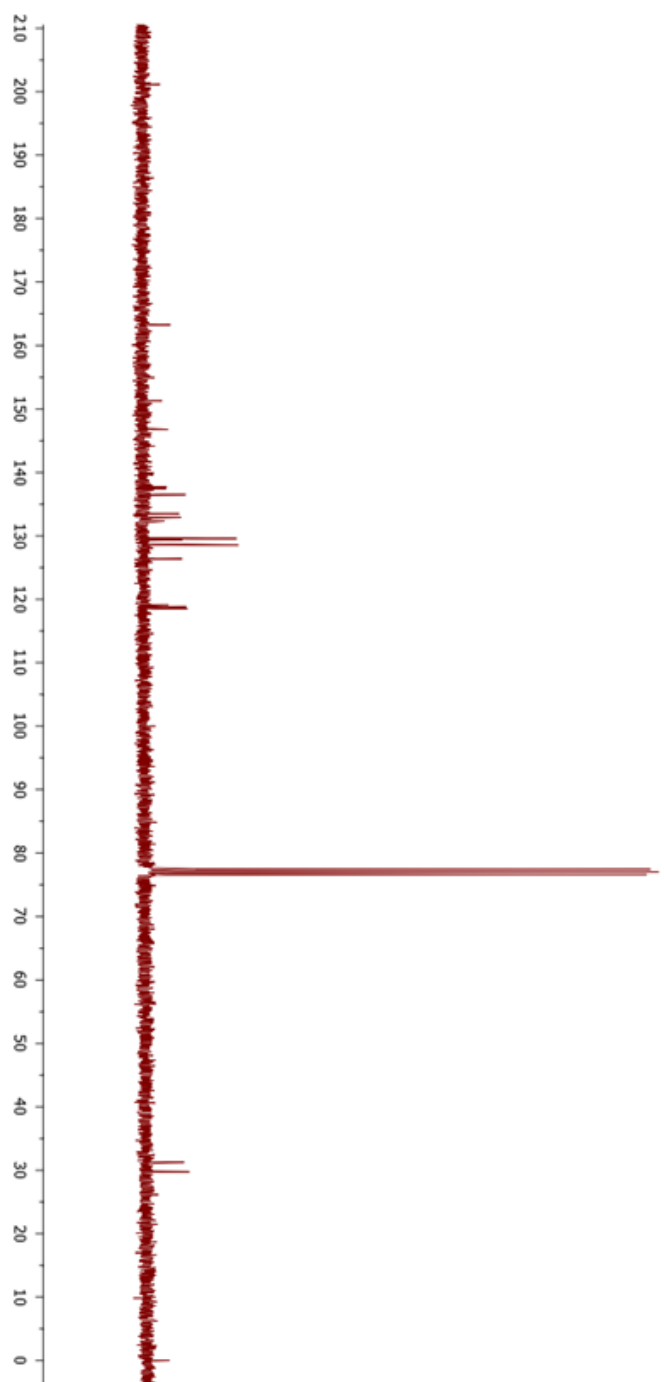
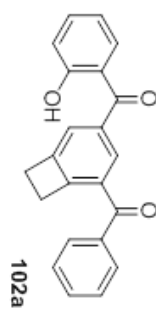
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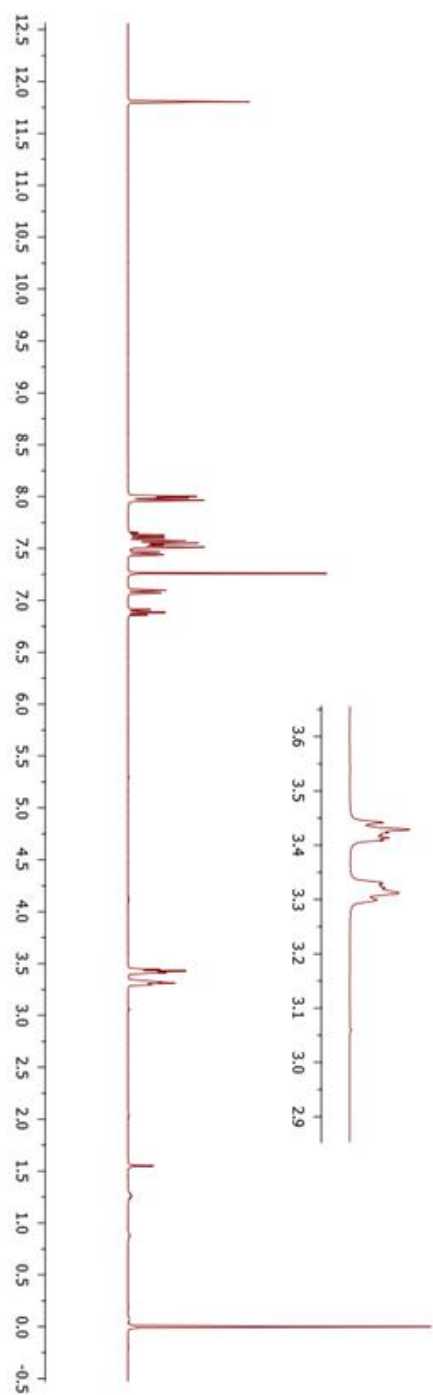
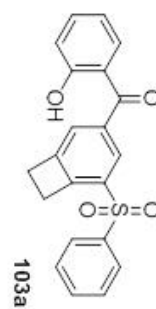
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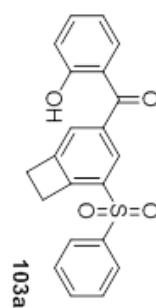
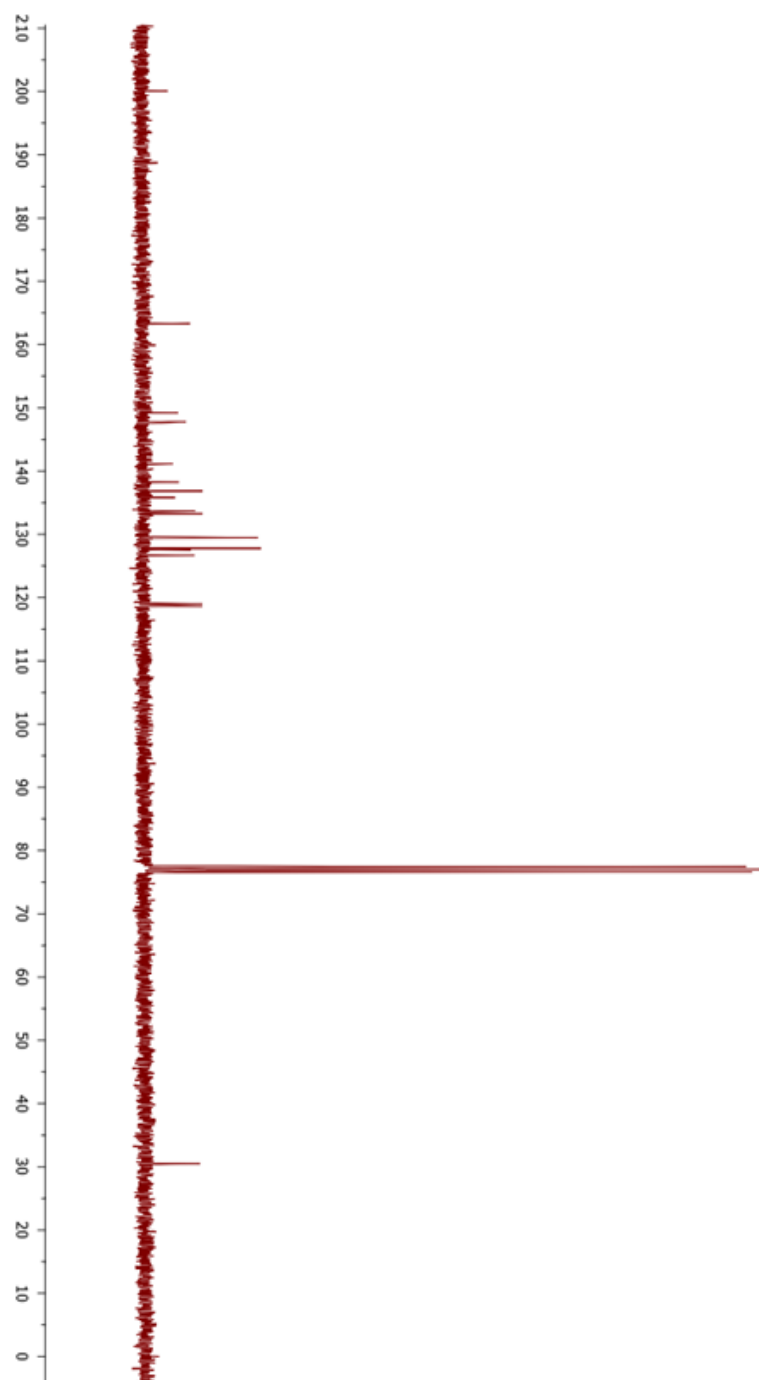
^1H NMR spectrum of **102a** in CDCl_3



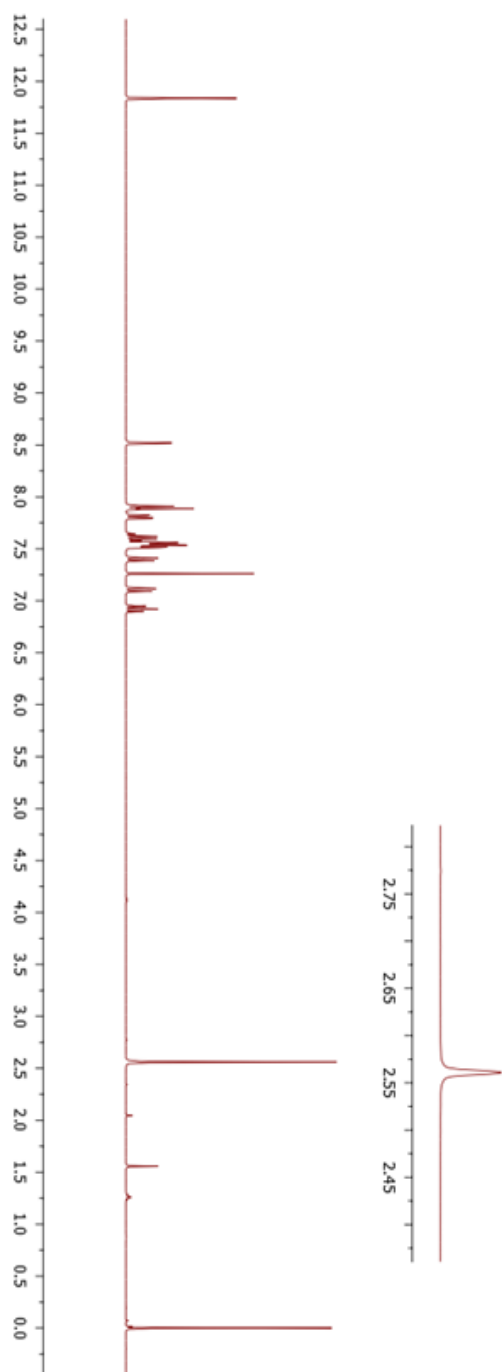
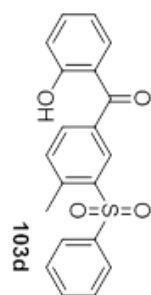
^{13}C NMR spectrum of **102a** in CDCl_3



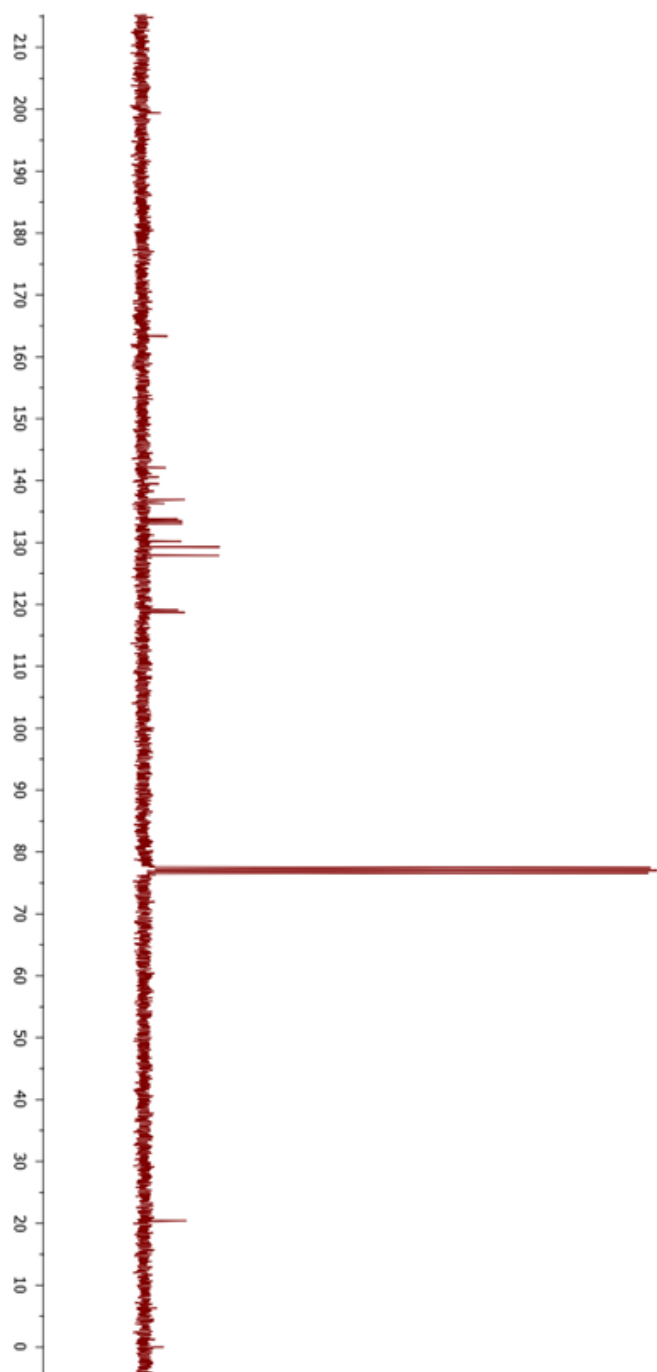
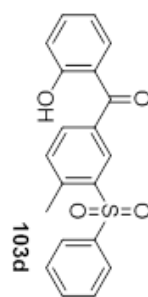
^1H NMR spectrum of **103a** in CDCl_3



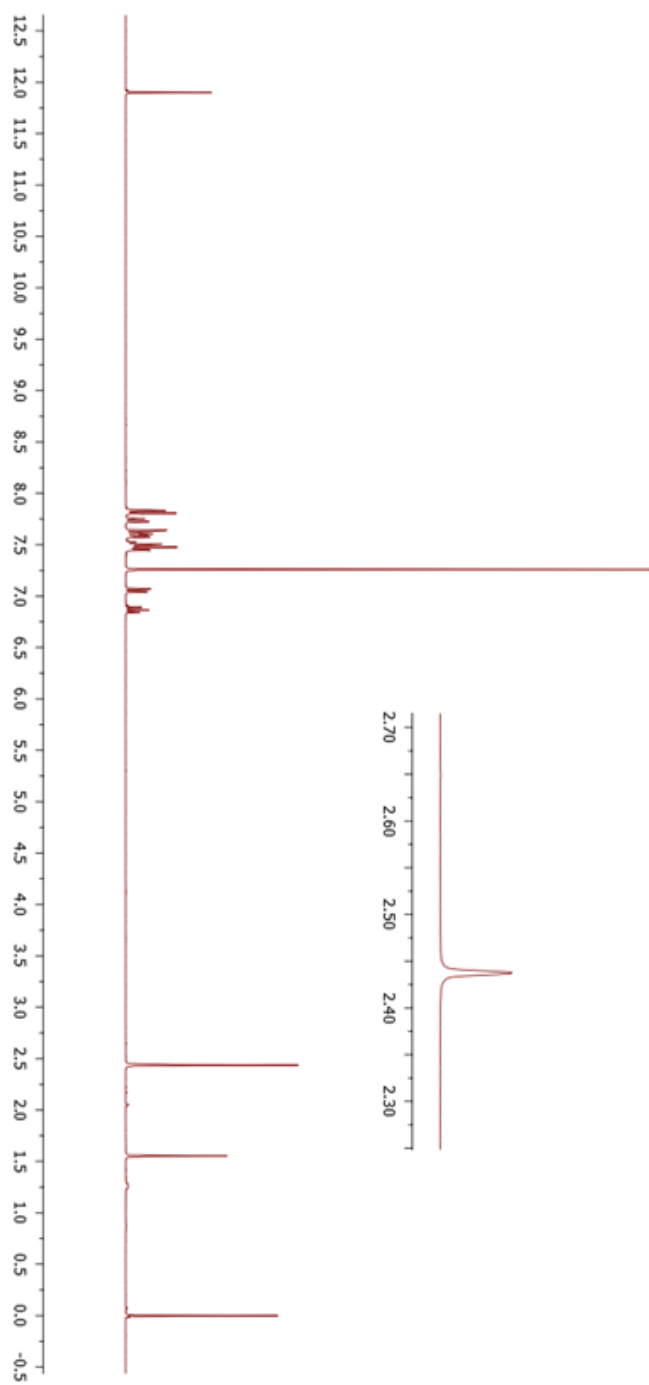
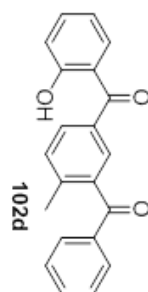
^{13}C NMR spectrum of **103a** in CDCl_3



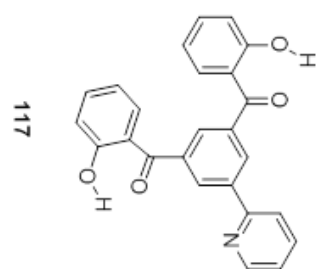
^1H NMR spectrum of **103d** in CDCl_3



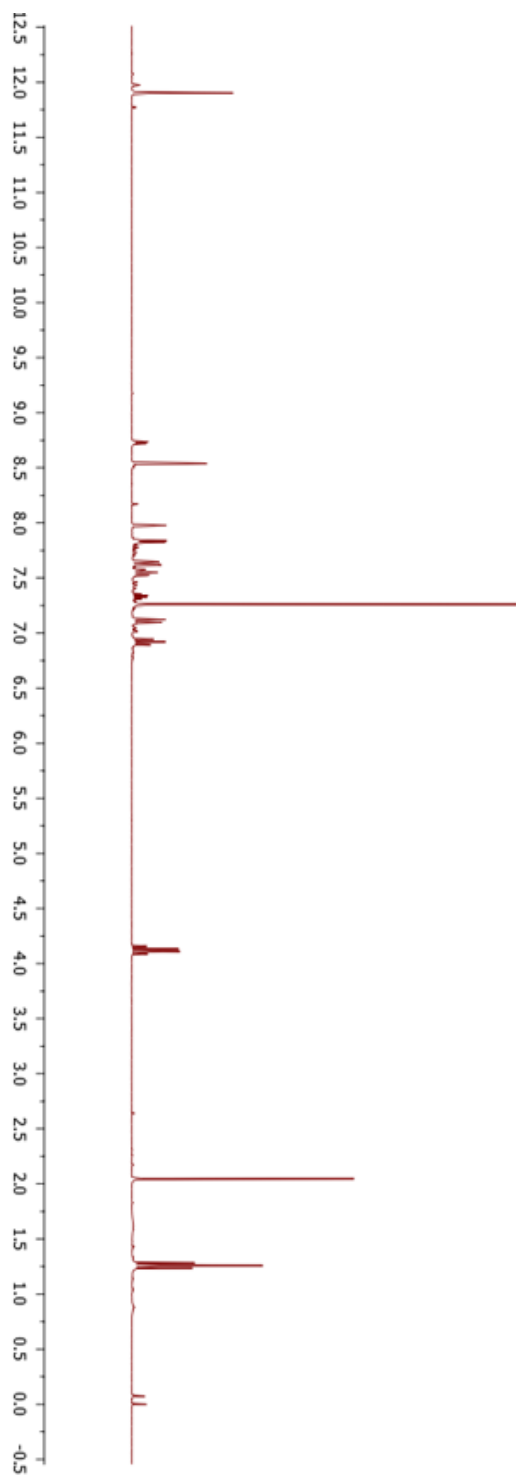
^{13}C NMR spectrum of **103d** in CDCl_3



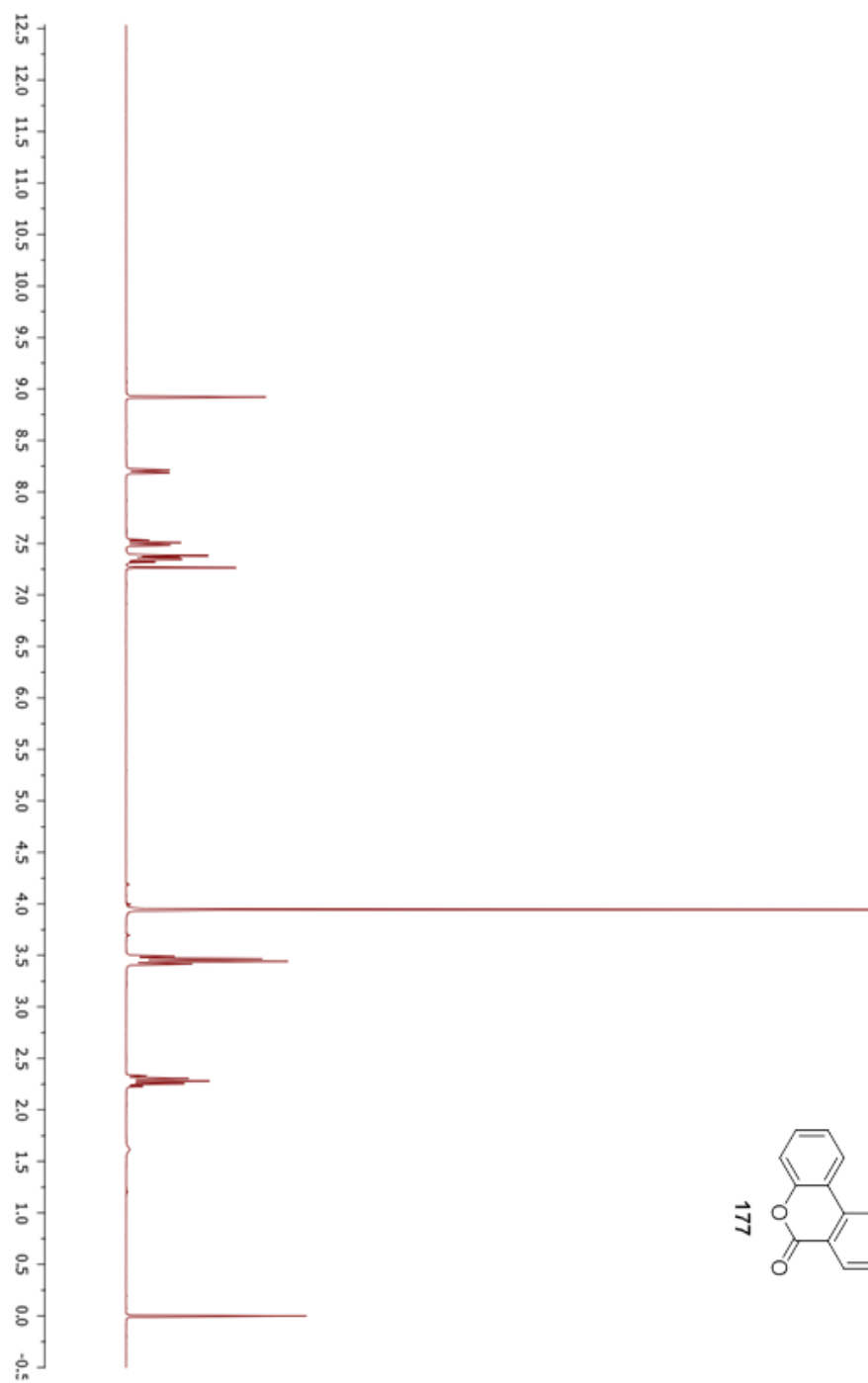
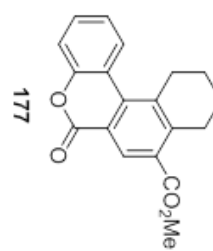
^1H NMR spectrum of **102d** in CDCl_3



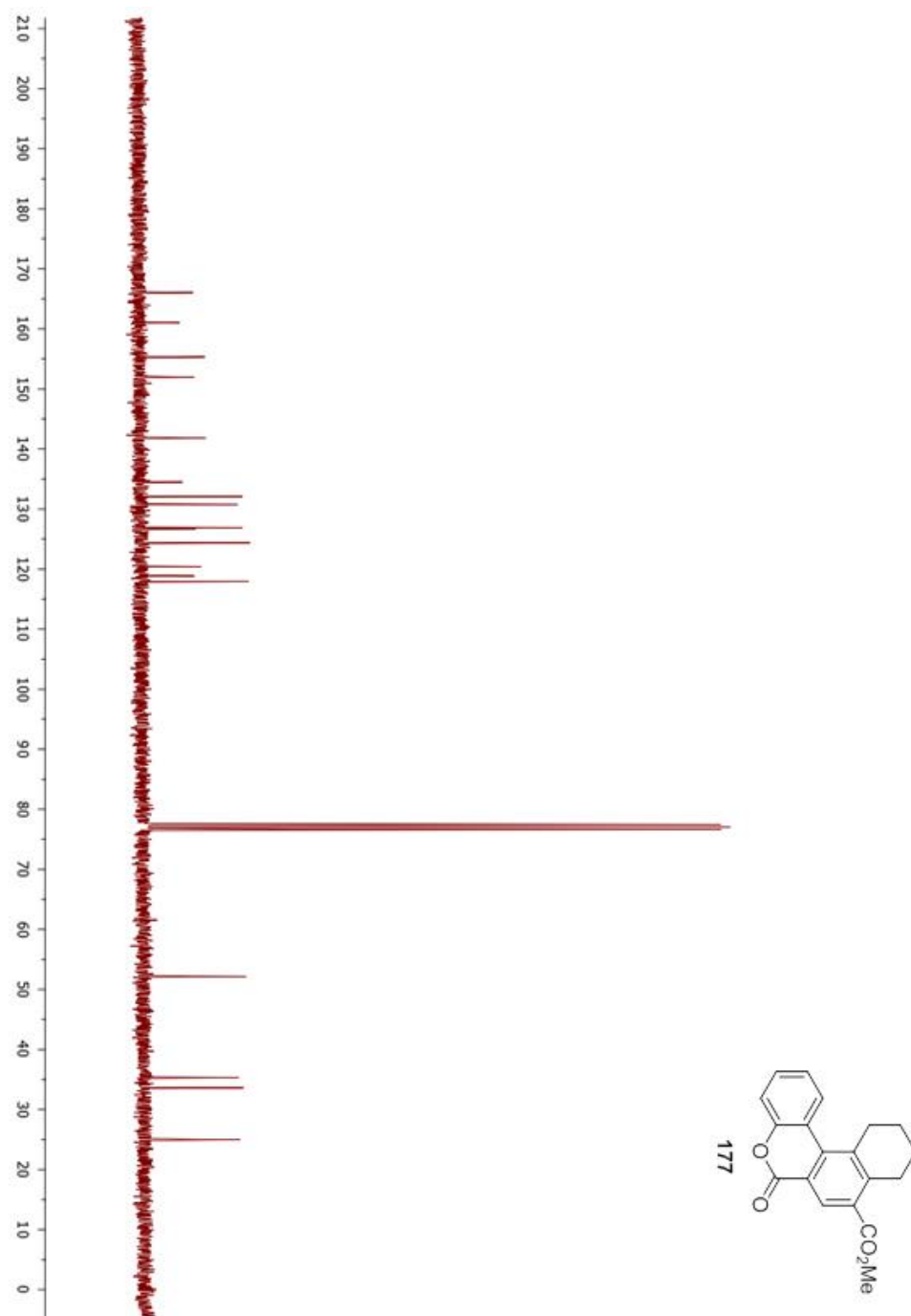
117



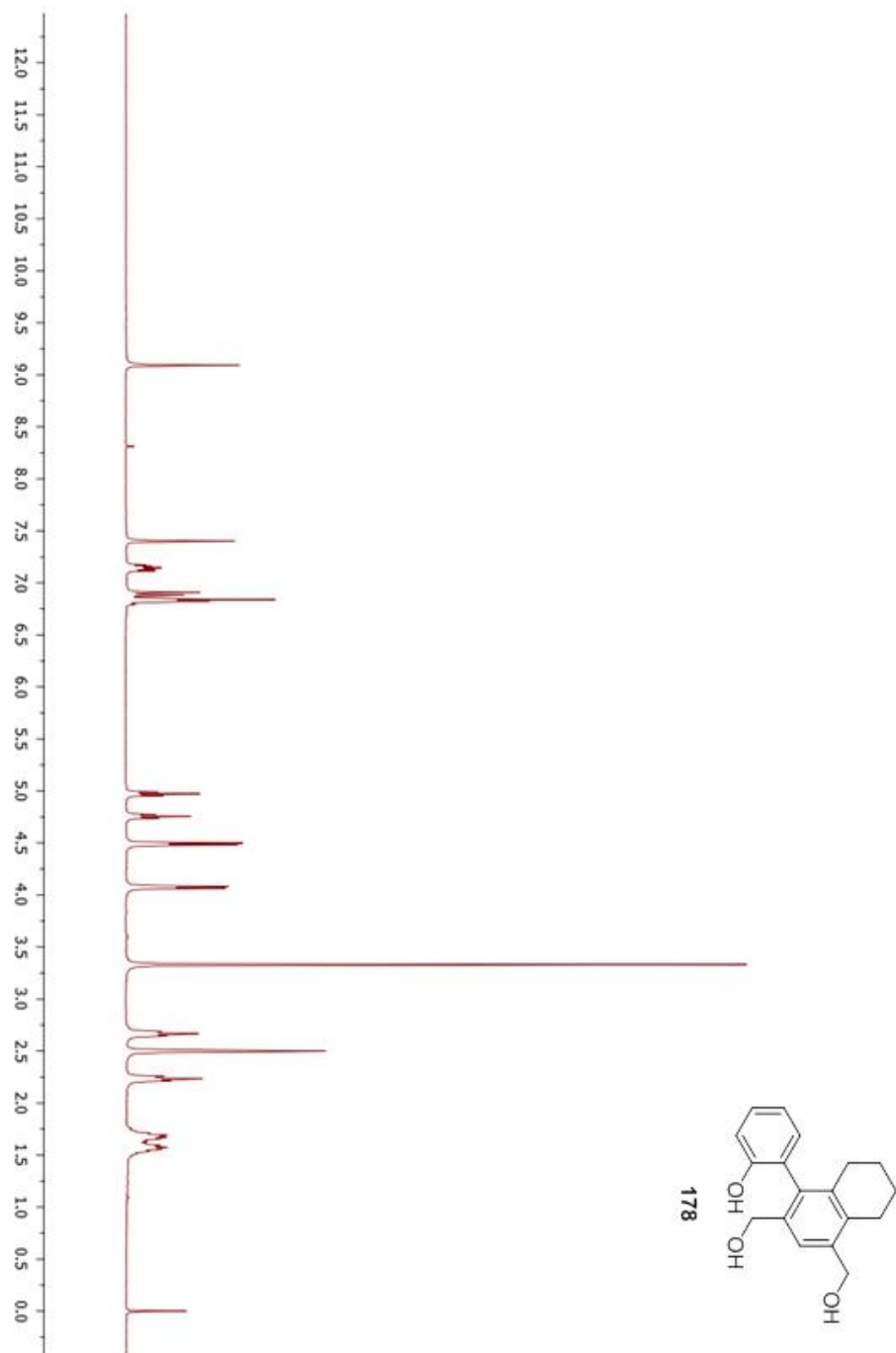
^1H NMR spectrum of **117** in CDCl_3



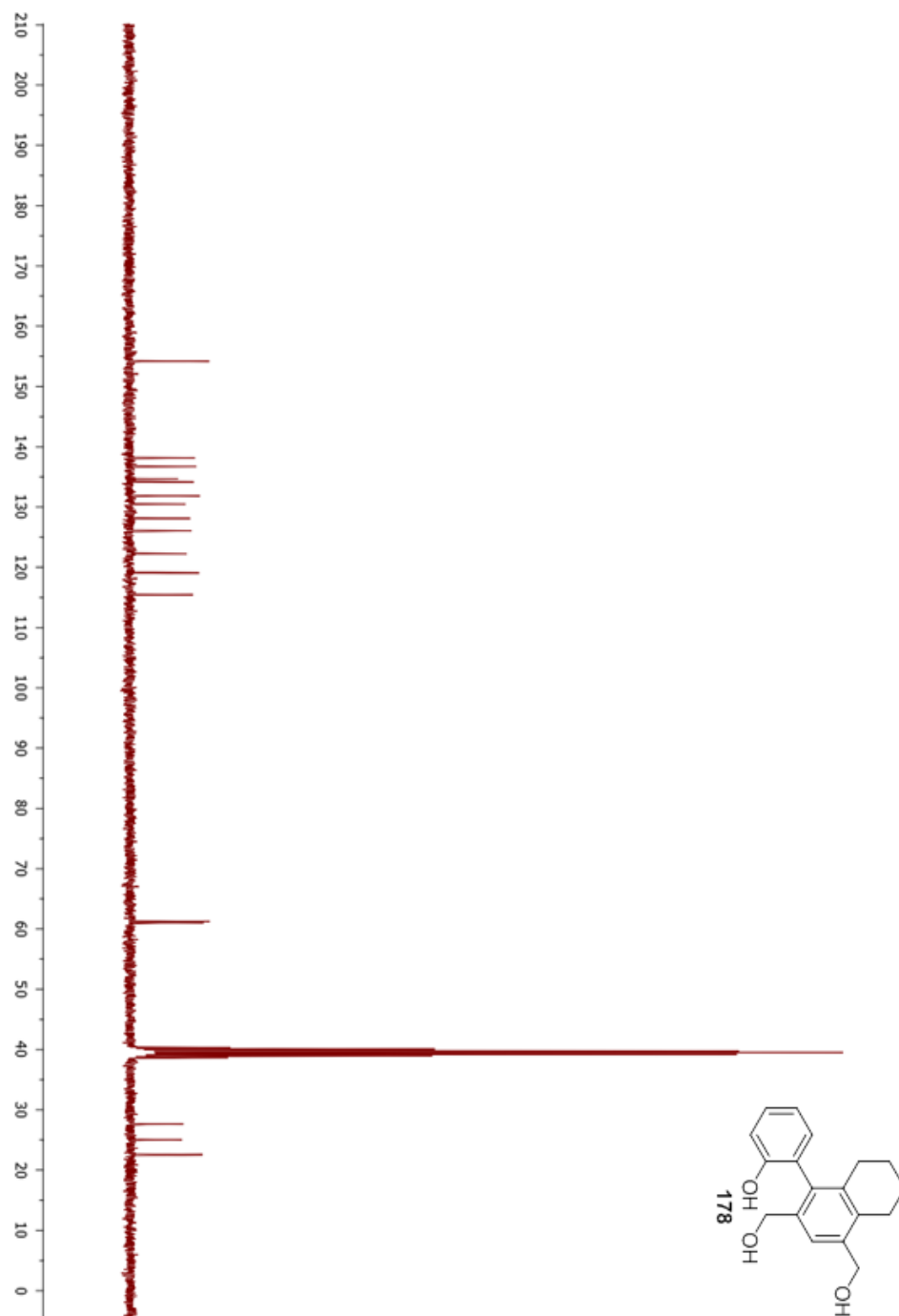
¹H NMR spectrum of **177** in CDCl₃



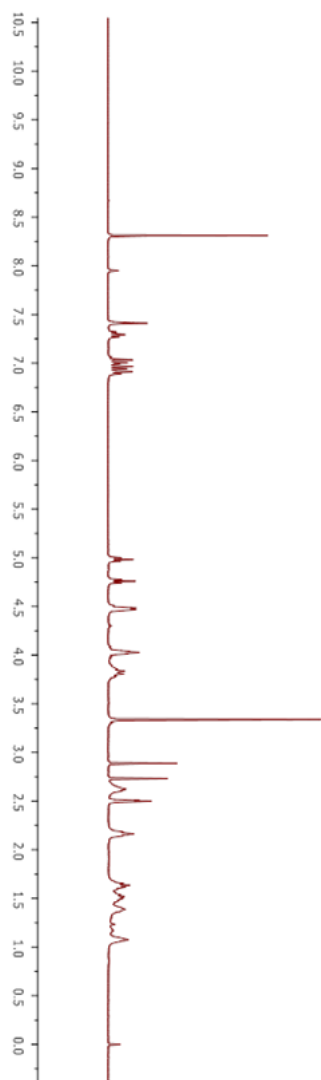
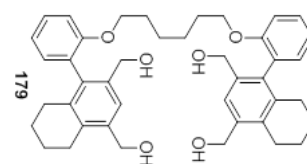
^{13}C NMR spectrum of **177** in CDCl_3



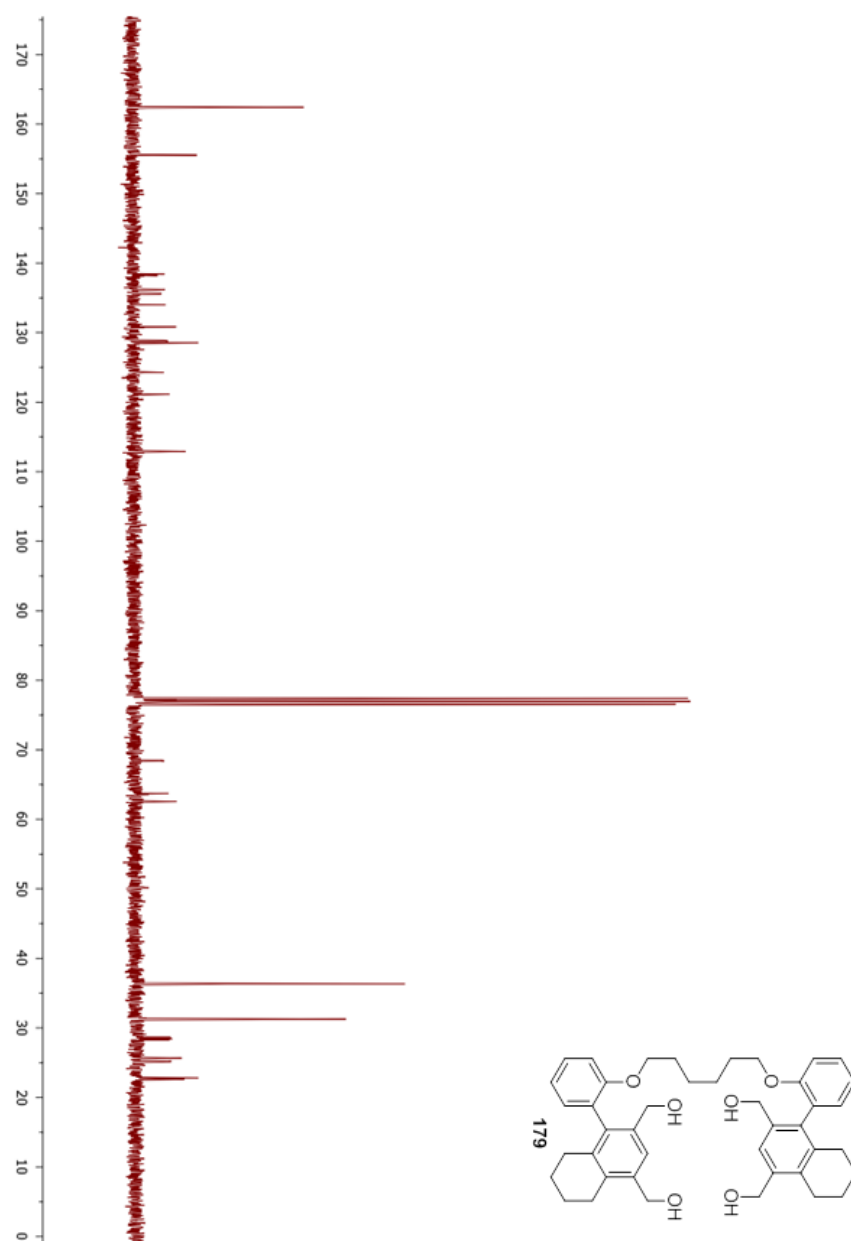
^1H NMR spectrum of **178** in DMSO



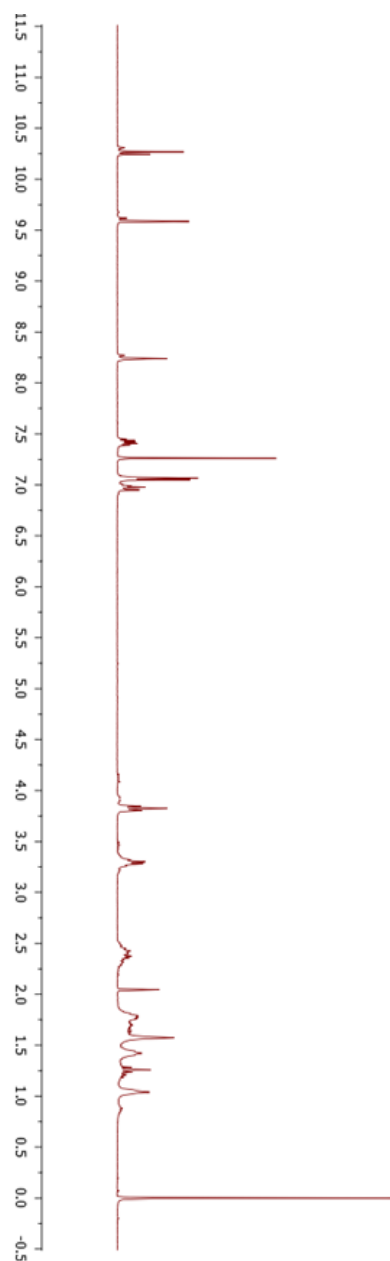
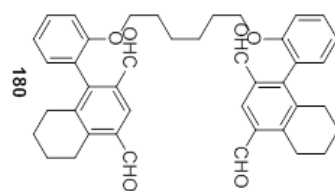
^{13}C NMR spectrum of **178** in CDCl_3



^1H NMR spectrum of **179** in CDCl_3



^{13}C NMR spectrum of **179** in CDCl_3



^1H NMR spectrum of **180** in CDCl_3

